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New (9th) Edition

**W. B. SAUNDERS CO., Philadelphia and London**

VOLUME 23

*Boston Number*

NUMBER 5

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THE  
MEDICAL CLINICS  
OF  
NORTH AMERICA

*SEPTEMBER, 1939*

PHILADELPHIA AND LONDON

W. B. SAUNDERS COMPANY

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PUBLISHED BY MONTHLY (SIX NUMBERS A YEAR) BY W. B. SAUNDERS COMPANY, WEST WASHINGTON  
SQUARE, PHILADELPHIA.

MADE IN U. S. A.



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*Boston Number*  
**THE MEDICAL CLINICS**  
OF  
**NORTH AMERICA**

Volume 23

September, 1939

Number 5

**CLINIC OF DR CHESTER S KEEFER**

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**SULFANILAMIDE**  
**ITS MODE OF ACTION AND SIDE EFFECTS**

**MODE OF ACTION OF SULFANILAMIDE**

As soon as it became evident that sulfanilamide influenced infections in animals and man, a great interest arose in the study of the mode of action of the drug *in vitro* and *in vivo*. Indeed there have been numerous studies of this matter, and on certain points there is general agreement, on others, the problem remains controversial and excites great interest. The disagreement is often due to the use of different methods and various strains of streptococci in the experiments which are planned to determine the mode of action of the drug.

An appreciation of the mode of action of sulfanilamide is more than a matter of academic interest, since if we know what can be accomplished by the use of this drug under optimum conditions, then we can define the scope of its use together with its limitations.

**Experimental Studies**—Insofar as the hemolytic streptococcus is concerned, it is fair to say that the main action of sulfanilamide is one of bacteriostasis. In order to demonstrate this action it is necessary to use small numbers of organisms and a concentration of the drug of at least 7 to 10 mg per 100 c.c. With some strains of hemolytic streptococci, the drug is bactericidal for small numbers of organisms, and this

is especially striking when the organisms are incubated at a temperature of  $41^{\circ}\text{C}$ .<sup>1</sup> It has been demonstrated that sulfanilamide does not inhibit the formation of hemolysin, erythrogenic toxin, or fibrinolysin, although it has been difficult to decide whether the actual amount of these substances are reduced in the cultures or not.

While the precise mechanism by which sulfanilamide exerts its effect on the organism is unknown, it is well to review what is known concerning this matter insofar as the application of this information to human infections is concerned. As already stated, the results have been conflicting in the hands of various students of the matter, but these differences can be explained in large part on a basis of the variation in both the methods and strains of organisms employed in the experiments. For these reasons it is necessary to review the results in accordance with the methods which were used.

**Broth Media**—When varying numbers of hemolytic streptococci are seeded in broth media which are free of peptone, sulfanilamide is bacteriostatic when the concentration is high (7–10 mg per 100 cc), the inoculum small, and the temperature for incubation  $37^{\circ}\text{C}$ . When the temperature is  $41^{\circ}\text{C}$ , it is often bacteriostatic for small numbers of organisms.

**Blood Serum**—The action of sulfanilamide in blood serum is bacteriostatic for all strains of hemolytic streptococci, and it is bactericidal for some types. In assessing the results, it is necessary to use adequate controls and serum from individuals who are free from infection, since Tillett<sup>2</sup> has shown that blood serum from some patients with acute infections is bactericidal for some strains of hemolytic streptococci. The bacteriostatic action of blood serum with leukocytes can be demonstrated by adding sulfanilamide to the serum directly *in vitro*, or it can be shown to be present in an individual who is receiving sulfanilamide by mouth, provided the concentration in the blood is above 7 mg per 100 cc.

**Whole Defibrinated Blood**—Rantz and I<sup>3</sup> have studied the action of sulfanilamide in whole defibrinated blood. The results of these investigations were of interest in light of the interpretation of the results of treatment in human infections. It was ascertained, first of all, that sulfanilamide always caused bacteriostasis when it was added to whole blood in concentrations of 5 mg per 100 cc or higher. In some samples of

whole blood there was a bactericidal effect which was always much more striking when the whole blood alone was capable of killing small numbers of organisms. In other words, the presence of antibody and sulfanilamide increased the bactericidal action of the system much more than could be demonstrated by either the antibody or the sulfanilamide alone.

These experiments suggest that the best results from sulfanilamide may be anticipated in man when an infection is present in an individual whose blood possesses antibody. In addition there are good reasons for believing that, when recovery takes place, it is through the cooperative activity of the drug and the normal defense mechanism of the body. This is perhaps the explanation for the fact that the drug produces its most striking effect in patients with localized infections in the presence of antibodies in their blood. It also explains why some patients who have bacteremia fail to show a dramatic clearing of the blood stream following sulfanilamide. In other words, it requires both a bactericidal mechanism and a bacteriostatic one to produce satisfactory results.

In a recent report concerning the action of sulfanilamide, Gay, Clark, Street, and Miles<sup>4</sup> reviewed the existing information concerning the mode of action of sulfanilamide in streptococcal infection. They stress the importance of considering the summation of all the factors which are responsible for favoring or inhibiting the growth of the streptococcus *in vitro* or *in vivo*. They point out once again that the main effect of sulfanilamide in the test tube is one of bacteriostasis and not an actual destruction of the organism. The degree of bacteriostasis depends in large part on the suspending medium. That is to say, the better the medium from its growth-promoting properties, the poorer the bacteriostasis will be when sulfanilamide is added. Conversely, the poorer the medium or the better its growth-inhibiting properties, the better the bacteriostasis. Indeed, in such a medium the addition of sulfanilamide frequently leads to death of the organism.

When the action of sulfanilamide against the streptococcus is studied in experimental animals, such as the mouse or the rabbit, the results must be assessed in accordance with the conditions that are known to exist when the streptococcus is introduced into these animals without sulfanilamide treatment. It is known that the conditions for the growth of the strepto-

is especially striking when the organisms are incubated at a temperature of  $41^{\circ}\text{C}$ .<sup>1</sup> It has been demonstrated that sulfanilamide does not inhibit the formation of hemolysin, erythrogenic toxin, or fibrinolysin, although it has been difficult to decide whether the actual amount of these substances are reduced in the cultures or not.

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coccus in both the mouse and the rabbit vary considerably, depending upon the strain of organism employed and the mode of infection. On the whole, however, if the proper strains are used, the animal is susceptible to infection. The natural defense mechanism comes into play so that phagocytosis of organisms by polymorphonuclear and mononuclear cells is attempted. It has been demonstrated by Gay and his associates<sup>1</sup> for the rabbit that recovery from hemolytic streptococcus infection follows when mononuclear cells accumulate in foci of infection and destroy the organisms. When animals that have been infected with streptococci are treated with sulfanilamide, phagocytosis is accelerated, the growth of the organism is inhibited, mononuclear cells accumulate, and recovery follows.

Gay and his associates were unable to show any change in the virulence of the strains they used in their experiments after the latter had been treated with sulfanilamide. They were, however, able to demonstrate that it did cause a temporary inhibition of hemotoxin formation. Leukocidin and fibrinolysin continued to be formed in the cultures. These observations are in general agreement with those of other investigators.

There are other studies which show that sulfanilamide does not inhibit antibody formation and does not, in itself, promote or increase phagocytosis. It does not neutralize toxin or soluble substances which are elaborated by the streptococcus.

**Summary**—For the present, then, one is justified in saying that recovery from hemolytic streptococcal infection probably occurs as the result of the combined activity of sulfanilamide and the immune mechanism. The sulfanilamide inhibits the growth of the organisms and perhaps kills small numbers of them. The immune mechanism limits the growth of the organism, localizes the infection, promotes phagocytosis, and finally destroys the organism. In other words, the sulfanilamide inhibits the growth of organisms and prevents overwhelming intoxication until the defense mechanism can be mobilized and finally bring about recovery.

#### THE TOXIC EFFECTS OF SULFANILAMIDE

Soon after sulfanilamide was used as a therapeutic agent it became apparent that it caused a number of side effects which could be attributed to the action of the drug. As ex-





perience accumulates, we are recognizing more and more the importance of these toxic reactions. I have summarized the important ones in Table 1, and the most important ones deserve separate comment.

**Skin Eruptions**—A wide variety of skin lesions have been described as a toxic reaction to sulfanilamide. They usually appear within seven to nine days after the drug is started. They are widespread and pleomorphic in character, erythematous, morbilliform, urticarial, or purpuric lesions may occur, or there may be a generalized exfoliative dermatitis. Associated with the skin eruption there may be generalized edema, high fever, leukocytosis (often reaching 70,000 or 80,000), transient jaundice without anemia, eosinophilia (20 to 55 per cent), and a generalized lymphadenopathy. One of the curious features of the skin eruption in some cases is that it is precipitated by sunlight, or at least it is often made worse by exposure to sunlight. Perhaps this is due to the disturbance in the metabolism of the porphyrins. These skin lesions often persist for a long period of time following the withdrawal of the drug.

**Fever**—Within four to fourteen days, usually seven to ten days, after the beginning of sulfanilamide treatment, fever varying between  $101^{\circ}$  and  $103^{\circ}$  F, or even higher, may occur and persist from two to nine days, usually two to four days. Very often there is an associated skin eruption, but in at least half the cases it may occur alone without any other signs of toxic manifestations of the drug. If a patient has had one febrile episode following the drug, he may have another soon after the drug has been started again. Jones and Miller<sup>7</sup> have observed this on two occasions, and during the second episode there was a sharp drop in the leukocyte count. Gallagher<sup>8</sup> has recently recorded a case in which fever appeared within twenty-four hours after the drug was started. This patient had had sulfanilamide a year previously and its administration had been followed by a skin eruption.

The recurrence of fever in a patient receiving sulfanilamide may be exceedingly difficult to interpret, since it may be an exacerbation of the disease or a sign of sulfanilamide intoxication. The time relations and the associated features of intoxication, together with the absence of signs of reactivation of the infection, are important features.

**Toxic Hepatitis**—Clinical and laboratory tests indicate that the liver function is disturbed in some cases of sulfanilamide intoxication. Thus, jaundice, enlargement of the liver, and a delay in the excretion of bromsulphthalein are found in a certain group of patients. Cases of toxic hepatitis have been described by Hageman and Blake,<sup>7</sup> Garvin,<sup>8</sup> Saphirstein,<sup>9</sup> Long,<sup>10</sup> and Fitzgibbon and Silver.<sup>11</sup> In three of the five cases reported by Garvin, various skin eruptions were present with the jaundice, and this was true of the case recorded by Saphirstein and the one by Myers, Vonder Heide, and Balcerski.<sup>12</sup> In most of these cases there was no associated anemia. Jaundice may also be observed in association with anemia. It is due to increased blood destruction and impaired liver function, since it can be demonstrated in some of the cases of anemia with jaundice that the bromsulphthalein test is impaired.

In short, one can say that toxic hepatitis is a feature of sulfanilamide intoxication and that it is accompanied by jaundice, enlargement of the liver and spleen, anemia, or exfoliative dermatitis. In rare instances ascites has developed. Fever is common, especially when there is anemia or exfoliative dermatitis. In several cases the signs of hepatitis appeared as long as forty-three days after the last dose of sulfanilamide. These cases are reminiscent of the cases of jaundice following arsphenamine in which the signs of intoxication appear some weeks after the last injection. In most of the reported cases of toxic hepatitis the prognosis has been good.

**Anemia**—Anemia following sulfanilamide is of two types (1) an acute hemolytic anemia, and (2) a slowly progressive hemolytic type. The first type was reported by Harvey and Janeway,<sup>13</sup> and since then similar cases have been reported by others. Wood<sup>14</sup> recorded the observations which were made in the Medical Clinic at the Johns Hopkins Hospital and found that 2.4 per cent of 378 adults and 8.3 per cent of 144 children developed the acute type of hemolytic anemia. I have observed two cases of the severe acute hemolytic anemia following sulfanilamide. The details of one of these cases follow.

**Case I.**—A woman with gonococcal arthritis receives sulfanilamide for three days, when she develops an acute hemolytic anemia. Recovery follows blood transfusions.

A woman fifty-two years of age, was admitted to the hospital complaining of a painful and swollen right knee joint. The onset of the illness

was abrupt Ten days before admission she developed pain in the ankles and about the right heel which continued for several days Then the pain appeared in the knee joint and was severe enough to require her to go to bed On the day following the onset of pain, the knee was swollen and she was advised to enter the hospital The past and family histories were non contributory

*Physical Examination*—This was essentially negative except for the monarticular arthritis involving the right knee joint, with evidence of acute inflammation and diffusion of fluid into the synovial cavity

*Laboratory Examinations*—The urine was normal in appearance and contained no increase in protein The blood showed a slight secondary

GC ARTHRITIS—HEMOLYTIC ANEMIA FROM SULFANILAMIDE

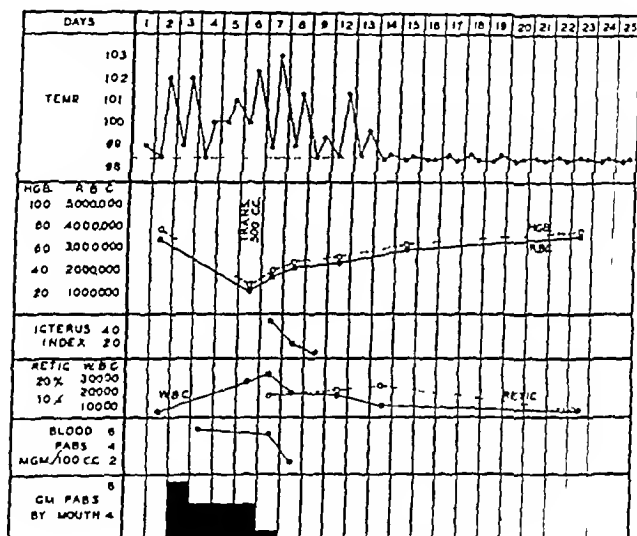


Fig 73—Clinical course in Case I

anemia, with a red blood count of 3,370,000 per cu mm., hemoglobin of 73 per cent, and white blood count of 9,000 per cu mm. A gonococcal complement-fixation test of the blood was positive. The synovial fluid was cloudy and yellow in appearance and contained 54,000 white blood cells, 95 per cent being polymorphonuclears. No organisms were cultivated on smear or culture.

*Course of Illness*—In view of the history, the monarticular arthritis, the character of the synovial fluid, and the positive gonococcal complement-fixation test, the patient was given sulfanilamide. This therapy was started on the third day of observation and continued for five days. The course of her illness is shown in Fig 73. It will be observed that she had irregular fever varying from 99° to 103° F. Three days after the exhibition of sulfanilamide

he developed a severe anemia with a fall in the red blood count to below 2,000,000 red cells and in the hemoglobin to 30 per cent. There was leukocytosis and jaundice. Following the withdrawal of sulfanilamide and a blood transfusion, recovery was prompt.

This case illustrates the course of events that is commonly seen during a hemolytic crisis following sulfanilamide. The main features are (1) the sudden onset of acute blood destruction appearing within three days of the beginning of its administration, (2) the rapid decrease in red blood cells and hemoglobin, which often progresses for two to three days in spite of the fact that the drug has been discontinued, (3) the continuation or exacerbation of fever during the stage of acute blood destruction, (4) the high leukocytosis, often reaching 30,000 to 50,000, (5) an increase in the urobilinogenuria, (6) slight clinical jaundice and hyperbilirubinemia, (7) hemoglobinemia, and, in some cases, (8) hemoglobinuria. During the period of recovery and blood regeneration there is an increased reticulocytosis and porphyrinuria.

In all the cases of acute hemolytic anemia that have been reported, the anemia appeared before the seventh day after the beginning of treatment, in most cases the maximum anemia is observed on the fifth and sixth days. It has not been observed before the third nor after the seventh day of treatment. There is no definite correlation between the amount of sulfanilamide administered, the amount in the blood, and the development of anemia.

For some unknown reason, children seem to be more susceptible and develop anemia more often than adults. Moreover, it has been pointed out by Wood<sup>14</sup> that patients who have developed anemia following sulfanilamide often suffer recurrences when a second course of the drug is given. Therefore, it seems wise to warn patients who have had such reactions that they should not take the drug again under any circumstances.

The slowly progressive anemia is, in my own experience, more common than the acute hemolytic anemias. Similar cases are recorded by Jennings and Southwell-Sander<sup>15</sup>. Naturally, in these cases it may be an exceedingly difficult matter to determine the relative importance of the sulfanilamide and the infection in the production of the anemia, but in many instances the anemia develops during the course of infections,

such as gonococcal urethritis, which are not usually accompanied by anemia

Thus there seems to be little doubt that the anemia in these cases is, at least in part, due to the sulfanilamide. In some I have observed splenomegaly accompanying the anemia, and this enlargement of the spleen may persist for several weeks after the drug is withdrawn. Finland, Brown, and Rauh<sup>16</sup> have recorded cases of anemia in pneumococcus meningitis following sulfanilamide, and stress this feature of sulfanilamide therapy.

The following case illustrates the slowly progressive type of anemia.

*Case II*—A young woman with hemolytic streptococcal cellulitis of the pelvic tissues and acute arthritis develops a slowly progressive anemia and splenomegaly following sulfanilamide. Recovery from anemia follows blood transfusions and withdrawal of the drug.

A young woman, twenty-two years of age, was admitted to the hospital on account of pains in the joints, abdominal pain, and high fever. Four weeks before admission she developed abdominal pain, leukorrhea, and a vaginal discharge which was copious in amount and which had an offensive odor. This was soon followed by an attack of pain in the right side of the abdomen, followed by vomiting. Examination of the patient at this time showed signs of a pelvic peritonitis with induration in the pelvic tissues on the right side. Several days after the onset of acute abdominal pain, she developed arthritis of both knee joints.

*Physical Examination*—This revealed a young woman, acutely ill, complaining of severe pain in the joints, particularly the knee. There was an erythematous papular, macular rash over the arms and legs and pain and tenderness over the lower half of the abdomen. Pelvic examination showed that the uterus was fixed, with marked tenderness and an ill-defined mass in the right adnexal region. There was also tenderness in the region of the left fallopian tube. There was profuse thick yellow discharge from the vagina and mild redness of the vulva. Both knee joints were tender to palpation. The left knee was markedly swollen with signs of fluid, and the left wrist was tender to palpation. The temperature was 103° F, the pulse 114, and the respirations 22.

*Laboratory Examinations*—The red blood cell count was 4,000,000 per cu mm and the hemoglobin, 90 per cent. Examination of the exudate from the cervix and uterus showed no gonococci, either by smear or culture, but there were numerous hemolytic streptococci present. A gonococcal complement-fixation test was negative on repeated occasions. Synovial fluid showed 62,000 white blood cells at the first knee tap and 32,000 at the second. The cells were all polymorphonuclears.

*Course of Illness*—At first it was thought that we were dealing with an instance of acute gonococcal pelvic inflammatory disease and gonococcal arthritis. However, in view of the fact that we were unable to isolate gonococci

from the cervical exudate or the synovial fluid and the gonococcal complement-fixation tests were negative in addition to the fact that we were able to isolate hemolytic streptococci from the vaginal discharge in almost pure culture, we were inclined to believe that the whole process was the result of a hemolytic streptococcal infection. Accordingly, the patient was given sulfanilamide, 6 gm a day for the first ten days during her illness. The temperature ranged between 100° and 102° F, the pulse rate between 100 and 110. Within the two-week period following the use of sulfanilamide the hemoglobin fell to 53 per cent. After a blood transfusion it rose to 64 per cent but within the next week it was again decreased to 50 per cent. With the development of anemia, the spleen became enlarged and was readily palpable two to four fingerbreadths below the costal margin. The spleen remained enlarged in spite of the transfusions and improvement in the anemia for a period of seven weeks. Gradually the patient's temperature returned to normal after three weeks had elapsed. The arthritis subsided without leaving any residual changes in the joints, and she recovered completely.

There were a number of features in this patient's illness which were difficult to interpret. In the first place, she had a pelvic infection with arthritis, but we were unable at any time to prove that this was due to the gonococcus. On the other hand, the evidence was convincing that we were dealing with a streptococcal infection of the pelvis. The use of sulfanilamide in relatively large doses was followed by gradual improvement but by no dramatic change in the course of her illness. She developed an anemia and splenomegalia, fever continued for three weeks, and it was only after the sulfanilamide was discontinued and several blood transfusions were given that the anemia disappeared. While it is possible that the anemia and the splenomegalia were the result of the hemolytic streptococcal infection, and it undoubtedly contributed to the anemia, it is suggestive, however, that sulfanilamide was responsible for at least part of the anemia and the splenomegalia. I have observed anemia and splenomegalia appearing in patients with infections which are usually not accompanied by either of these.

**Hemoglobinuria**—In cases of acute hemolytic anemia, hemoglobinuria may be a feature. It was first described by Kohn,<sup>17</sup> and we have observed a very striking case. Hemoglobinemia is present more often than hemoglobinuria and it is to be taken as a manifestation of increased destruction of blood. When acute hemolytic anemia occurs, the urine should be kept alkaline, since the presence of an acid urine may cause precipitation of the hemoglobin in the kidney tubules with ob-

struction and renal insufficiency. When the blood destruction is over, the hemoglobinuria disappears very rapidly.

**Agranulocytosis, Neutropenia**—Leukopenia has been observed following sulfanilamide in a number of cases, and the reports of Shecket and Price,<sup>18</sup> Johnston,<sup>19</sup> Jones and Miller<sup>5</sup> have included personally observed cases and reviews of other reported cases of agranulocytosis.

This complication is by far the most serious of all the toxic manifestations of the drug since the fatality rate is high, in the neighborhood of 80 per cent. An analysis of the recorded cases brings out several points of significance. The usual time of appearance of agranulocytosis has been recorded between the sixth and the thirty-fifth day after the administration of the drug, in most cases, however, it is between the fourteenth and twenty-first day of the disease. In a few, the leukopenia has been observed several days after the drug has been discontinued. In the cases recorded by Jones and Miller,<sup>5</sup> neutropenia and fever developed following the second attempt to resume treatment in a patient who had had two previous attacks of fever and generalized aching following its exhibition.

The following case illustrates the course of events in a patient who developed agranulocytosis following sulfanilamide treatment for gonococcal arthritis.

**Case III**—A woman with gonococcal arthritis developed agranulocytosis following ten days of sulfanilamide treatment. Death occurred six days later.

A young woman, forty years of age with gonococcal arthritis which was proved by isolating the gonococcus from the exudate in the synovial fluid, was given sulfanilamide in 4 gm. amounts daily. This was continued for eight days when an erythematous skin eruption appeared and the white blood cell count was found to be 2,700 with 62 per cent polymorphonuclears, 36 per cent lymphocytes, and 2 per cent monocytes. Sulfanilamide was discontinued immediately. On the following day the white cell count was 1,700, and the smear showed only 1 per cent polymorphonuclear leukocytes and 99 per cent lymphocytes. Two days later the patient began to complain of a sore throat, had high fever, and was extremely ill. In view of the absence of polymorphonuclear leukocytes in the differential blood smear and the leukopenia, 40 c.c. of pentnucleotide were given intramuscularly on the second day. Fluids were forced by mouth and parenterally, and two 300 c.c. blood transfusions were given. In spite of this treatment ulcerative, necrotic lesions appeared in the throat and the mucous membranes of the mouth and lower lip. The patient became progressively worse and died four days after the onset of the agranulocytosis and fifteen days after the beginning of treatment with sulfanilamide.

Necropsy showed superficial ulceration of the posterior pharynx and epiglottis, moderate enlargement of the lymph nodes of the neck, and acute arthritis in the ankles, knees, elbows, and wrists

In this case agranulocytosis developed on the ninth day after the sulfanilamide was started. The other sign of intoxication from the drug was the presence of a skin eruption. Once the agranulocytosis appeared, infection developed, the disease progressed rapidly, and the patient died four days after the appearance of the infection.

It should be pointed out that in a number of cases of agranulocytosis which have been reported the drop in the leukocyte count appears quite suddenly, very often after the first week of the illness. For these reasons the white cell count should be done repeatedly while the patients are receiving large amounts of this drug. Agranulocytosis is by far and away the most serious complication of sulfanilamide therapy.

**Splenomegaly**—One of the features of the slowly progressive anemia which appears following sulfanilamide is the development of splenomegaly. The spleen is firm and may extend 2 to 5 cm. below the costal margin and remain enlarged for three to five weeks after the blood has returned to normal. Obviously, in some infections the splenomegaly may be difficult to differentiate from the acute splenic tumor that is a feature of the disease. However, the occurrence of splenomegaly in a patient who has an infection which is usually not accompanied by enlargement of the spleen, the presence of anemia, and cyanosis are all features which suggest that the splenomegaly is a response to sulfanilamide treatment. Rimington<sup>20</sup> has called attention to the enlargement and engorgement of the spleen of animals receiving large doses of sulfanilamide and the presence of marked engorgement and abundant deposition of iron-staining granules and of brownish iron-negative amorphous pigment in the cells of the pulp.

I have observed splenomegaly in patients receiving sulfanilamide for gonococcal, streptococcal, or urinary tract infections, and in all instances there has been an associated anemia. From the experimental observations of Rimington and from my own clinical observations, there seems to be no doubt that the splenic enlargement in these cases is dependent upon the sulfanilamide therapy.



**Cyanosis.**—Blueness of the skin and mucous membranes following the administration of sulfanilamide is exceedingly common, in fact, when large amounts of the drug are given it is almost always present. There are two main views concerning the cause of the cyanosis following sulfanilamide (1) that it is due to the presence of methemoglobinemia, rarely sulfhemoglobinemia, and (2) that it is due to the presence of a black or bluish-black pigment which is derived from sulfanilamide. Inasmuch as it was first pointed out by Ottenberg and Fox<sup>21</sup> that exposure of a colorless solution of sulfanilamide to ultraviolet light changed it to a bluish-purple, it was suggested that this pigment might be responsible for the cyanosis. It has been shown, however, that this pigment is not directly responsible for the cyanosis, but that it is due to the presence of methemoglobinemia. Moreover, the administration of methylene blue causes the cyanosis to disappear by abolishing the methemoglobinemia.

**Porphyrimuria**—It has been reported by Rimington and Hemmings<sup>22</sup> that sulfanilamide causes an increased excretion of porphyrins in the urine, and further studies by Rimington stress the fact that while there is no parallelism between the therapeutic efficiency of sulfanilamide and other related compounds and their porphyrimuric action, there is a correlation between the capacity of these drugs to produce porphyrimuria and then toxicity. The presence of large amounts of porphyrin in the blood or tissues may account for the sensitivity to sunlight which is present in some of the patients receiving sulfanilamide, and also for the rare cases of peripheral neuritis which are encountered.

**Summary**—It is gathered from a study of the side effects of sulfanilamide that a wide variety of symptoms and signs may appear. During the first week, cyanosis, nausea and vomiting and the acute hemolytic anemias are important. During the second week, fever, skin eruptions, and toxic hepatitis, and during the third week, agranulocytosis and a slowly progressive anemia, may be features. To be sure there is some overlapping of the time at which most of these features appear but, in general, the pattern is as outlined above. If one bears this in mind, one can be prepared for the appearance of various reactions at different periods in the treatment.

In summing up, then, one can say that sulfanilamide is a

most valuable drug in the treatment of a variety of infections. Its principal action seems to be the inhibition of the growth of organisms, and recovery probably takes place when this drug is given through the cooperative activity of both the drug and the normal defense mechanism of the body. In general it can be said that the drug produces a number of side effects which may be extremely disagreeable for the patient and, in some instances, very dangerous. Since many of the toxic manifestations come on suddenly, all patients who are receiving this drug should be under careful observation and supervision so that the proper management and treatment may be started at once.

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# SULFANILAMIDE IN THE TREATMENT OF HEMOLYTIC STREPTOCOCCAL INFECTION

## INTRODUCTION

It has now been established beyond any question that sulfanilamide is a most valuable therapeutic agent in the treatment of hemolytic streptococcal infection in man. One can demonstrate that it reduces the fatality rate in cases of hemolytic streptococcal infection associated with bacteremia, in meningitis, and in puerperal sepsis. It shortens the duration of the disease in many cases of erysipelas and acute tonsillitis, and it is an effective agent in the treatment of chronic ulcers of the skin and chronic osteomyelitis due to this organism. The drug has very little influence upon the eruption in scarlet fever, and it does not prevent the development of recrudescences of rheumatic fever or nephritis following a hemolytic streptococcal infection. In several small series of cases sulfanilamide has been used in preventing recurrent attacks of tonsillitis in rheumatic subjects. There is also some evidence that its routine use in patients with otitis media may actually reduce the number of cases of acute mastoiditis. In some series of cases in which the drug was given to patients with scarlet fever, a number of pyogenic complications seem to have been reduced.

It has been ascertained from the study of large numbers of cases that, in order to produce the best results with this drug, it is necessary to bring the organisms into contact with adequate concentrations of the drug, and it is necessary for the body to develop or maintain an active immune mechanism which will localize the infection and finally destroy the organisms.

Before presenting a case which illustrates the effect of sulfanilamide on the course of diseases produced by hemolytic streptococcal infection, it is desirable to review some of the facts concerning this group of infections in general, especially the pathogenesis of these infections together with their prognosis and the mechanism of recovery, insofar as it is known.

It is now well established that the normal habitat of the hemolytic streptococcus is in the lymphadenoid tissue of the throat. It does not grow freely on the surface of the mucous membranes, but is found in the crypts of the tonsils and in the lymphoid tissue itself. About 30 or 40 per cent of all normal individuals carry hemolytic streptococci in their throats at some time during the course of the different seasons of the year, the incidence being higher in the winter and early spring months when hemolytic streptococcal infections are present in the community. The presence of these organisms in the human throat may be a transitory phenomenon, or they may be found over long periods of time without causing disease. Carriers are much more common among individuals who are in contact with patients with acute streptococcal infection of the throat, and such persons are especially liable to become carriers if they have a common cold. Moreover, there is evidence that carriers can spread organisms much easier when they have a cold. In the study of many groups of patients with hemolytic streptococcal infection, one will find transient carriers, permanent carriers, patients with subclinical infection, and patients with clinical infection.

From the study of serologic groups and types of hemolytic streptococci, it has been found that not all of the strains of hemolytic streptococci in man are capable of producing disease. For example, the only group of strains that are important are those designated as Group A, which can be recognized by appropriate serologic study. Organisms that fall into Groups B, C, F, G, H, and K are of no significance insofar as human disease is concerned, but they may give rise to confusion when throat cultures are made for the purpose of detecting carriers.

Any hemolytic streptococcus that is found in the throat, then, should be studied for its group specificity since only those falling into Group A are of any consequence.

#### THE ANTIGENIC STRUCTURE OF HEMOLYTIC STREPTOCOCCI

In an attempt to understand the antigenic structure of human, virulent Group A hemolytic streptococci, many studies have been made of the various components of the whole organism as well as the soluble products that are produced during their growth in suitable media. Many of the components of

this group of organisms are antigenic, others are haptenes and carry either type or group specific characteristics. The structure of Group A hemolytic streptococci is summarized in Table 1.

TABLE 1  
STRUCTURE OF HEMOLYTIC STREPTOCOCCUS, GROUP A

Components.	Capable of producing antigenic response.	Remarks
Whole organism	Yes	
M substance (protein)	No (haptene)	Type specific
C substance (carbohydrate)	No (haptene)	Group specific.
Nucleoprotein	Yes	Not species specific, overlaps with pneumococci and other organisms
Erythrogenic toxin (A and B)	Yes.	Neutralized by antitoxin
Hemolysin	Yes	
Fibrinolysin	No	
Leukocidin	?	

#### IMMUNITY TO HEMOLYTIC STREPTOCOCCI

Hemolytic streptococci are destroyed in the body by means of intracellular digestion. This is greatly facilitated by the presence of specific antibody and complement which favor and promote phagocytosis. There are good grounds for believing that the macrophage, the histiocyte, and the cells of the reticulo-endothelial system are of greater importance in the destruction of hemolytic streptococci than the polymorphonuclear cells.

In order for destruction to take place, then, it is necessary for the immune processes of the body to develop antibodies which will prepare organisms for phagocytosis and destruction. Aside from these antibacterial antibodies, other antibodies, such as antitoxin, antihemolysin, and antifibrinolysin, are elaborated and aid in the localization and fixation of organisms in the tissues.

#### THE MECHANISM OF RECOVERY FROM HEMOLYTIC STREPTOCOCCAL INFECTION

While our information concerning the mechanism of recovery from hemolytic streptococcal infection is far from com-

plete, one can say that, in general, recovery occurs when the infection is localized, the organisms are prevented from spreading, their growth suppressed, and they are finally killed. This complicated mechanism is the result of the summation of a number of processes, which include the products of inflammation aiding in the localization of infection, the anatomic structure of the area of infection, the presence or absence of specific antibody, and an infection which is due to an organism that is virulent or avirulent in the sense that it can resist or succumb to phagocytosis in normal whole blood. When infections remain localized, there is evidence that in many instances the organism causing the infection can be phagocytized by leukocytes of the normal individual. Apparently this can take place without the presence of antibodies in the serum, or at least it can be said that the blood of such individuals does not contain antibody in excess of the normal non-infected individual.

Since it can be shown that there is no correlation between the time of recovery and the development or increase in the antibody content of the blood in patients who have a local streptococcal infection, it has been postulated that recovery from a local infection is due to the inflammatory reaction, which aids in fixation and the local immune process which is carried out by the tissue and wandering cells. When there is a spreading infection with bacteremia, one usually finds that the infection is due to an organism which cannot be phagocytized by normal human leukocytes, which are derived from most individuals, and that there is an absence or only a low titre of antibody in the circulating blood. One may find, however, that there is bacteremia if the local defense mechanism is ruptured, as sometimes occurs following trauma to a localized infection. In patients with general infection, recovery usually occurs when the blood is cleared of organisms, the process is localized, and there is a general antibody response which assists in preventing spread of the infection to distant organs.

It need not be seen, then, that any measure which aids in suppressing the growth of organisms and localizing the infection would be of assistance in the treatment of these infections.

## PROGNOSIS

In appraising the various factors which influence prognosis in hemolytic streptococcal infections, it is necessary to take into consideration the age, the type and location of the lesion, the presence or absence of bacteremia and debilitating disease, and the type of treatment. The mortality in these infections is highest in the first, third, and seventh decades. This corresponds, respectively, to the peaks of incidence of infections occurring in the throat, of puerperal infections, or of infections such as cellulitis or erysipelas. In the first decade the highest incidence of death is seen in infants and children under four years of age, especially when there is erysipelas or middle-ear mastoid disease with its intracranial and other complications. In the cases of puerperal infection, the death rate is highest in those with peritonitis, thrombophlebitis, and bacteremia. In erysipelas, the seriousness of the infection increases with age. In general it may be said that streptococcal infections are most serious at the two extremes of life, in the very young and in the aged.

Of all the prognostic signs, the presence or absence of *bacteremia* is probably the most reliable. The prognosis is always grave when bacteremia is present, regardless of the age of the patient, but there is a tendency for bacteremia to increase in seriousness with advancing age and with its occurrence during the course of erysipelas or cellulitis, regardless of age. The fatality rate in the presence of bacteremia is somewhat lower in puerperal sepsis than in erysipelas or cellulitis, and is lowest of all in the first two decades of life when the primary infection is situated in the throat or middle ear or mastoid processes. When recovery occurs in the patient with bacteremia, it can be shown that the blood is invaded for a relatively short time and then cleared of organisms, with or without the subsequent development of focal metastases to various organs. Where such metastases can be adequately treated by physical methods, recovery usually takes place. On the other hand, if death occurs, there usually has been a rapidly progressive bacteremia without focal metastases or with focal metastases in such areas as the endocardium or meninges, or multiple abscesses which cannot be treated by surgical methods.



## TREATMENT

From the foregoing discussion it is gathered that the ultimate goal in the treatment of streptococcal infections is to localize the infection, suppress the growth of organisms, and finally destroy them. In the preceding paper\* it was pointed out that sulfanilamide inhibited the growth of organisms but that, in most instances, there was no evidence that the bacteria were actually destroyed. Final destruction of the organisms was accomplished by the general defense mechanism of the body, so that it is highly likely that the administration of sulfanilamide to a patient with hemolytic streptococcal infection slows up the growth of the organisms and, in this way, allows the general defense mechanism more time to produce antibodies before it can be overwhelmed or rendered ineffective.

The following case illustrates a number of these points in the treatment of hemolytic streptococcal infection with sulfanilamide.

**Case I.**—A young woman develops hemolytic streptococcal bacteremia following acute follicular tonsillitis. Bacteremia persists for four weeks. Treatment is with large doses of sulfanilamide and repeated blood transfusions. Recovery.

A twenty-eight-year-old white woman, who was seven months pregnant, developed acute rhinitis one week before admission to the hospital. Several days later there was difficulty in swallowing, pain in the throat and swelling of the cervical lymph nodes. Within two days after the onset of sore throat, she began having repeated chills and high fever. The family and past histories were non-contributory.

Physical examination showed an acutely ill young woman who was restless but mentally clear. Her temperature was 104° F, pulse 120, and respirations 30. The skin was warm and moist, the tonsils were moderately enlarged but not injected. There were a few pea-sized, soft, tender glands in the superior cervical chain on both sides of the neck. There was no induration or tenderness over the jugular vein. The neck was not stiff. The breasts were enlarged, consistent with a seven months' pregnancy. The heart was not enlarged, the rate was rapid, and the sounds were clear. The lungs were clear throughout to auscultation and percussion. The abdomen was distended and the uterus was enlarged, also consistent with a seven months' pregnancy. The fetal heart was heard plainly in the right lower quadrant. The extremities were normal.

Laboratory examination showed that the urine contained a small amount of albumin and the sediment was negative. The red blood cell count was 4,200,000, the hemoglobin 80 per cent, and the white blood cell count 30,700.

\* Keefer, C. S. Sulfanilamide. Its Mode of Action and Side Effects. MED. CLIN. N. A., 23: 1133 (Sept.), 1939.

Blood culture showed numerous colonies of hemolytic streptococci. Throat culture showed many Beta hemolytic streptococci and a few hemolytic *Staphylococcus aureus*. X-ray of the chest revealed a small patch of bronchopneumonia at the left base. One week later the X-ray showed a diffuse bronchopneumonia at both bases.

The clinical course, as far as the temperature and therapy are concerned, is shown in Fig. 74. It will be noted that bacteremia persisted for over two weeks in spite of large doses of sulfanilamide and blood transfusions. Following the premature delivery of a seven-months-old baby, the blood cultures became negative and remained so during the entire period of observation.

HEMOLYTIC STREPTOCOCCUS SOPSIS FOLLOWING TONSILLITIS — PREGNANCY

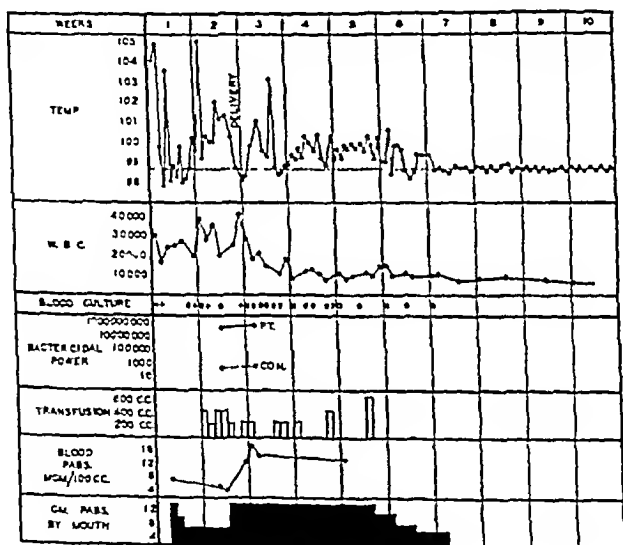


Fig. 74—Clinical course in Case I.

One of the extraordinary features of this patient's illness was the fact that, at the time of delivery, the patient's blood culture and cultures from the placental blood and the lochia all contained hemolytic streptococci, yet the baby survived and showed no signs of acute infection whatsoever.

The unusual feature of this case was the presence of hemolytic streptococcal bacteremia following acute tonsillitis without evidence of the local focus of suppuration and without the development of suppurative foci of infection in any part of the body in spite of the fact that there was a bacteremia for over two weeks. During the first two weeks of observation the sulfanilamide did not appear to influence the course of the disease.

Following the birth of the child, the blood cultures became negative. When the blood was studied for the presence of anti-bacterial antibodies, as noted in the chart, it was found that antibodies were present. This encouraged us to continue the use of sulfanilamide in large doses and blood transfusions in order to combat a rapidly progressive anemia.

There seems to be little doubt that the original portal of entry for the hemolytic streptococcus was in the throat, and similar cases are not infrequent. They are described as examples of post-tonsillitis sepsis or post-anginose sepsis or sepsis following angina. In most of the cases of this type of sepsis, the outcome is extremely grave since, in many instances, there is a thrombophlebitis of the deep tonsillar veins and multiple metastases in various organs.

This case serves to emphasize the fact that large amounts of sulfanilamide should be given to these patients and, if anemia develops, the latter should be treated by blood transfusions. Moreover, transfusions should be given in an attempt to supply antibody until potent specific sera are available for treatment.

**General Plan of Treatment**—In any hemolytic streptococcal infection, sulfanilamide should be used promptly, and especially at an age period when the prognosis is likely to be poor or when the infection is localized in a region where it is apt to spread to important structures or invade the blood stream.

The question of *dosage* is a very important matter in treatment, since it is essential that the optimum effect be obtained. From all the evidence at hand it is desirable to give enough of the drug to produce maximum bacteriostasis. This can be accomplished in our experience by giving enough of the drug to produce a concentration of at least 7 to 10 mg per 100 cc in the circulating blood. In some instances higher concentrations may be necessary, but such cases are unusual. It is well, then, to give at least 6 to 8 gm (90 to 120 grains) during the first twenty-four hours and then 4 gm of the drug every day until the optimal effect has been obtained.

The blood should be examined for the development of an anemia or leukopenia. The occurrence of an *anemia* is very common following the use of the drug, but unless it is an acute

hemolytic anemia, it is not an indication for discontinuing the drug. That is to say, if the infection is of a serious nature (bacteremia, peritonitis, meningitis), the drug should be continued and the patient given repeated blood transfusions.

The presence of a normal white blood count or leukopenia associated with an acute infection is not a contraindication to the use of the drug. Indeed, one often sees an increase in the leukocyte count following the use of sulfanilamide. *However, when the drug is given to patients with leukopenia or a normal white blood cell count, the blood count must be followed with great care.* The development of leukopenia following sulfanilamide is always dangerous.

#### SUMMARY AND CONCLUSIONS

One may sum up the treatment of hemolytic streptococcal infections with sulfanilamide by saying that the drug should be given early in the course of the illness and in amounts which are adequate to produce optimal effects. The patient must be observed carefully for the appearance of signs of intoxication, and when they arise, prompt action must be taken.



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### SULFANILAMIDE IN MENINGOCOCCIC INFECTIONS

SINCE the experimental work of Buttle, Gray and Stephenson,<sup>1</sup> showing that sulfanilamide gave protection from meningococcic infections in mice, and of Proom,<sup>2</sup> showing protection from a million minimal lethal doses both in types I and II if treatment was given at once, extensive experiences and experiments have been reported. Whitby<sup>3</sup> reported a mortality of 16.6 per cent in treated mice as against 72 per cent in controls. Levaditi and Vaisman<sup>4</sup> also found mice strikingly protected by sulfanilamide, and less so by other members of this group of drugs, and that results appeared in from six to eight hours, with rapid disappearance of the meningococci from the peritoneum in from twenty to forty hours.

Schwentker, Gelman and Long<sup>5</sup> first reported the treatment of human meningococcic meningitis, in ten cases with one death. They also treated successfully a case of meningococcemia. They used the drug intrathecally at twelve- to twenty-four-hour intervals. The meningococci were cleared from the spinal fluid, usually in twenty-four hours and in all cases within three days.

Bernstein,<sup>6</sup> Mitchell and Traschler,<sup>7</sup> McIntosh, Wilcox and Wright,<sup>8</sup> Weill-Halle, Cochéme and Lautman,<sup>9</sup> Weill-Halle, Myer and Tiffenau,<sup>10</sup> Armand-Dehille, Lestroquoy and Tiffenau,<sup>11</sup> Tixer,<sup>12</sup> Darré, Zagdoun and Oemischn,<sup>13</sup> Basman and Perley,<sup>14</sup> Morton, Ewing and Ebsworth,<sup>15</sup> and Craddock,<sup>16</sup> reported cases, usually treated also with serum, with extraordinary good results.

Carey<sup>17</sup> reported five cases treated with sulfanilamide alone by various routes with recovery.

Banks,<sup>18</sup> in a comparison of serum and sulfanilamide, found in thirty-eight cases treated with serum a mortality of 16 per

cent, in fifty-nine with serum and sulfanilamide 11.8 per cent mortality, and in sixteen with sulfanilamide alone a mortality of 6.25 per cent. However, he advocated combined serum and sulfanilamide treatment.

Waghelstein,<sup>19</sup> in a final analysis of results at Sydenham Hospital, first reported by Schwentker et al.,<sup>5</sup> reported with sulfanilamide alone in seventy-two cases a mortality of 15.27 per cent, with serum and sulfanilamide combined a mortality of 23.52 per cent in thirty-four cases, and in serum-treated cases only a mortality of 26.9 per cent in 368 cases. If deaths within twenty-four hours were excluded, the death rate was 11.59, 13.33 and 16.71 per cent, respectively. Waghelstein preferred the oral treatment. On the other hand Eldahl<sup>20</sup> treated twelve cases of meningococcic infection with daily intrathecal injections, with a 25 per cent mortality. He considered oral treatment ineffective. Willien<sup>21</sup> treated five cases (with recovery) intrathecally and by mouth or by subcutaneous injection.

Meningococcemia cured by sulfanilamide has been reported by Zendel and Greenberg<sup>22</sup> and by Krusen and Elkins.<sup>23</sup> In the latter, serum treatment had been unsuccessfully used for two weeks.

Jewesbury<sup>24</sup> reported six cases, with recovery, treated with sulfanilamide and also with soluseptasine and prontosil rubrum, and Crawford and Fleming<sup>25</sup> treated ten cases, with one death, with intramuscular neoprontosil and sulfanilamide by mouth, whereas in thirty cases in which serum treatment was employed the mortality was 80.7 per cent. They reported one case in which the patient was not benefited by oral therapy and intramuscular injections of neoprontosil but who rapidly improved with intrathecal administration of sulfanilamide.

The most extensive experience with sulfanilamide (lysococcine) is reported by Muraz, Chirle and Quequiner<sup>26</sup> from French Nigeria. Their results were striking, particularly under the conditions of remoteness of many of the patients from medical centers and attention. Their results are given in Table 1.

In a total of 348 cases treated with sulfanilamide the mortality was 11.2 per cent. The dosage by mouth was 1.2 gm 4 i d for two days and half this dose 4 i d for the next six to ten days, totaling about 30 gm for adults and not exceeding

TABLE 1

TREATMENT OF CEREBROSPINAL MENINGITIS (Muraz, Chirle and Quequiner)

	Cases	Deaths	Mortality, per cent.
Serum treated	49	11	22.44
Serum and sulfanilamide by mouth	23	2	8.7
Sulfanilamide intraspinally and by mouth	54	8	14.8
Sulfanilamide by mouth alone	271	29	10.7

45 gm Intrathecal treatment, 10 to 20 c c of 0.8 per cent solution (5-10 c c less than the fluid withdrawn at each lumbar puncture), was given once or twice at intervals of from twenty-four to forty-eight hours (or longer because of the circumstances) followed by 1.3 to 3 gm 4 i d by mouth for about one week. They used rubiazol (carboxy-sulfamide chrysoidine) in four cases, with two deaths.

In our series, all patients with meningococcic infection admitted to the South Department, Boston City Hospital, from April 1, 1937, to June 30, 1938, were treated with sulfanilamide by mouth, without serum. Three patients received subcutaneous treatment for one day because of vomiting, two received neoprontosil and one sulfanilamide.

Twenty-five patients during this period were admitted showing meningococci by blood or spinal fluid culture or by smear. Two other patients showing primary acute purulent meningitis with spinal fluid cell counts of 6440 and 7780 were also treated successfully, but these two cases are not included as meningococci were not demonstrated.

These cases were of the usual severity and showed the characteristic picture. Thirteen patients were delirious, disoriented, or comatose, and nine were drowsy but oriented and rational. There was the characteristic cloudy fluid with increased pressure, protein and polynuclear leukocytes and decreased sugar. In twelve of the cases blood cultures were positive for meningococci and, in ten, were negative. In eighteen cases, spinal fluid cultures showed meningococci and, in six, were sterile. Nine patients showed meningococci in both blood and spinal fluid. Unless the culture conditions are such that meningococci are recovered in the first culture in sulfanilamide-treated cases, there is a strong probability (70



per cent) that none will be found because of the rapid clearing. The dosage of sulfanilamide varied according to age from 60 to 120 grains daily at four-hour intervals and was approximately from 1 to 2.5 grains per pound of weight per day. In the later cases the first dose was often large, 60 to 80 grains, and then the usual doses at four-hour intervals were given. The duration of treatment was long because of lack of knowledge as to possible recurrence. In the earlier cases it was from five to thirty days, averaging 14.3, later it was six to nineteen days, averaging 10.4 days.

Side-effects were infrequent in spite of the large and long continued treatment. About half the patients were cyanotic, and one patient had a late, moderately severe hemolytic anemia requiring omission of treatment but not requiring transfusions. Three patients had sulfanilamide eruptions. No malignant neutropenias were seen.

### RESULTS OF TREATMENT

Of the twenty-five patients, three died, or a fatality rate of 12 per cent. These three deaths occurred nineteen, twenty-seven and thirty-two hours after admission. Two patients

TABLE 2  
MENINGOCOCCIC MENINGITIS MORTALITY IN MASSACHUSETTS

Year	Cases	Case rate per 100,000	Deaths	Mortality per 100,000	Mortality rate, per cent.
1926	116	2.8	39	0.9	33.6
1927	95	1.8	43	1.0	57.3
1928	107	2.5	38	0.9	35.9
1929	167	3.9	79	1.9	47.3
1930	174	4.1	59	1.4	33.9
1931	101	2.4	30	0.7	29.7
1932	85	1.9	34	0.8	41.0
1933	50	1.2	25	0.6	50.0
1934	66	1.5	28	0.6	42.4
1935	83	1.9	55	1.3	66.3
1936	205	4.7	100	2.3	48.7
1937	166	3.8	72	1.6	43.4
1938	59	1.3	18	0.4	30.5

were sixteen years of age and had a rapidly developing severe infection of less than a day's duration, the other patient was a fifty-seven-year-old man who was picked up in the

street unconscious and in whose case no data could be secured. These patients received a total of from 50 to 125 grains of sulfanilamide, undoubtedly treatment would have been much more vigorous had these patients been seen today.

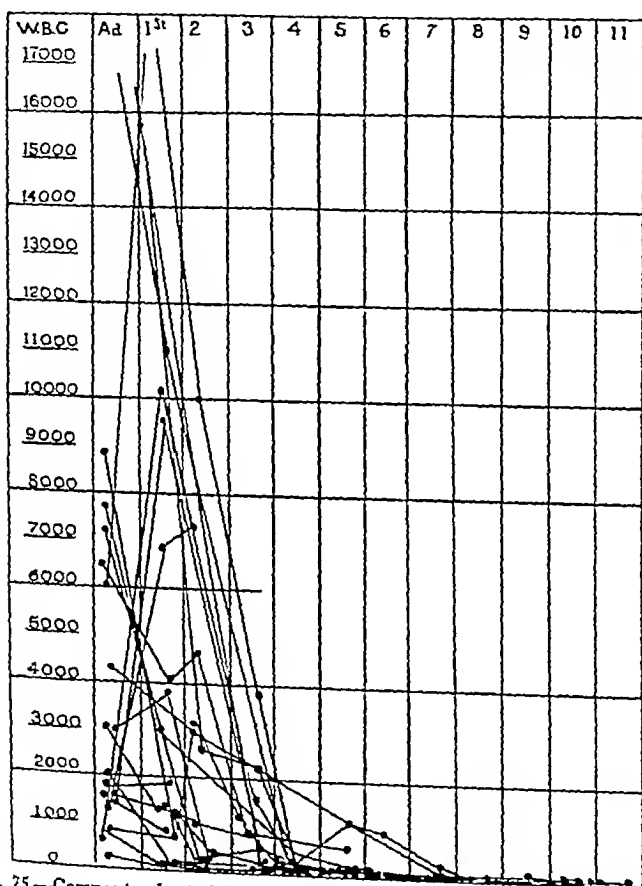


Fig. 75—Composite chart showing trend of spinal fluid cell count according to day of treatment.

Interpretation of mortality data is difficult because of the variation in the severity of the condition, in the patients' ages, and in time of treatment. There was no selection of cases in this series, all patients being treated by the same methods. In the preceding period, from February 29, 1936, to April 1, 1937, forty-four patients were treated vigorously with serum,

with a mortality of 47.7 per cent. The mortality from meningococcus meningitis in Massachusetts in 1936 was 48.7 per cent and has averaged about 43 per cent for the past ten years (Table 2).

The ages of the patients admitted after the institution of chemotherapy dropped so that the number of aged patients was much reduced. The mortality is highest in infants and especially in old persons. In the sulfanilamide-treated cases in which the patients were under twenty years of age, the mortality was 11.1 per cent as compared to serum-treated cases in which it was 25 per cent. Josephine Neal<sup>27</sup> reported a mortality in 1279 cases, of patients treated with serum and who were under twenty years of age, of 27.2 per cent and in 237 cases between ten and twenty years of age of 20.5 per cent. Hoyne<sup>28</sup> reported 118 cases treated intraspinally and intravenously with serum (patients under twenty) with a mortality of 15.2 per cent and in a series treated only by intravenous therapy at these ages the unusual mortality of 2.3 per cent. The results here are in accord with Muraz, Chirle and Quequener's,<sup>26</sup> with a mortality of 10 per cent in 271 cases, and with those of Waghelstein,<sup>19</sup> with a mortality of 15.27 per cent in forty-two cases treated by sulfanilamide by mouth.

TABLE 3

MENINGOCOCCUS POSITIVE CULTURES FROM SPINAL FLUID AFTER BEGINNING TREATMENT

Days	Serum treated	Sulfanilamide treated
2	3	4
3	4	2
4	4	0
5	2	1
6-10	8	0
11	1	0
21	1	0
25	1	0

More striking evidence was the rapid clinical improvement even in apparently moribund cases and the rapid bacterial clearance of the spinal fluid (Fig. 75). In only seven of our cases could meningococci be obtained after the first day of treatment, one for five days, two for three days and four for

two days By contrast, in the serum-treated group, meningococci were obtained from the spinal fluid in 40 per cent after the first day and up to twenty-five days (Table 3)

Relapse occurred in one serum-treated case, none in the sulfanilamide cases

The complications were somewhat less marked in the sulfanilamide group Cerebrospinal block, which occurred to some degree in 20 per cent of the serum-treated cases, was absent. Lumbar punctures were done daily, every other day or occasionally at longer intervals up to eleven days, averaging 5.5 per patient. A rapid drop in protein, cells and pressure occurred, as reported by Hannah and Hobson<sup>32</sup> The protein showed a slower and less regular fall than the leukocytes, and the rise in sugar also varied moderately. In only two cases did lumbar puncture seem at all indicated to relieve pressure, and we would agree with other observers that it is not of important therapeutic value in sulfanilamide-treated as contrasted with serum-treated cases (Table 4)

TABLE 4  
COMPLICATIONS

	Serum treated	Sulfanilamide treated
Bronchopneumonia	4	3
"Cord bladder"	4	1
Neuritis of extremities	4	0
Cranial nerve damage	3	1
Transverse myelitis	2	0
Hemiplegia	2	0
Meningococcal arthritis	2	2
Epididymitis	1	0
Septic phlebitis	1	0
Uveritis	1	0
	<hr/> 24	<hr/> 7

The type and virulence of the organisms was not determined because of laboratory difficulties In our cases, just preceding, occurring in the same general area type I was found in nine cases, type I-III in four cases, type II in two cases and agglutinating type I-II-III in two cases, as determined by Dr Branham Virulence tests for mice done at the Massachusetts State Health Department Laboratory varied from very high to low

There was no definite effect of time of starting treatment on recovery, two of the fatal cases being started at the end of

the first day and one being unknown. In the very fulminating cases, unless the patients were admitted during the first or second day, death occurred before such patients could be brought to the hospital.

#### COMMENT

While judgment of the relative efficacy of any treatment based on mortality statistics is made difficult in this disease by lack of comparable controls, the accumulated experience in France, England and America leaves no doubt of the great value of sulfanilamide therapy. In a total from the literature of 136 cases receiving some form of sulfanilamide therapy and serum, there was a mortality of 13.9 per cent, and of 510 cases so treated but without serum the mortality was 11.4 per cent.

Chemotherapy is not dependent on the agglutinative type of meningococcus and apparently is equally effective in virulent or less virulent cases if administered in time. It is possible that some strains of the meningococcus may be less susceptible to the drug, but this has not been demonstrated in clinical work. Branham and Rosenthal,<sup>20</sup> comparing serum and sulfanilamide in experimental infections in mice, found three strains against which sulfanilamide was more effective, four strains in which serum was more effective, and three in which there was no difference. There is a belief suggested by some evidence that long continued low dosage may induce or favor a state of resistance of the meningococci to the drug, but proof of resistant strains is lacking.

In one of our cases, during preliminary studies before the institution of chemotherapy routinely, it was found that in six days of sulfanilamide treatment no clinical or bacteriologic benefit was noted although 525 grains of the drug had been given. Following a single dose of antimeningococcic serum (8 c.c. intracisternally), rapid recovery and bacterial clearing of the spinal fluid occurred. The spinal fluid concentration was not determined. Possibly a higher dose or simply more prolonged chemotherapy might have been equally successful. Long and Bliss<sup>41</sup> cite two similar cases in their experience. No drug-resistant cases were encountered after the routine chemotherapy was established, although such resistance to serum is not infrequent.

Experimentally, in mice, it has been shown by Branham and Rosenthal<sup>29</sup> and Brown<sup>30</sup> that combined serum and sulfanilamide was more effective than either alone. This opinion has been held by Banks<sup>18</sup> and Neal<sup>31</sup> and by others.

The accumulating clinical evidence strongly suggests that chemotherapy alone, if adequately used, is efficient and that serum is usually unnecessary. There are grounds for belief, both from serum studies and from the evidence from chemotherapy, that intrathecal serum at least may cause some definite harm. Banks,<sup>18</sup> and also Tixer,<sup>12</sup> feel that intrathecal serum is definitely harmful and, with intravenous serum combined with sulfanilamide, unnecessary.

In the choice of the chemotherapeutic agent there is apparently some latitude. Whitby<sup>3</sup> from an experimental viewpoint stated that proseptasine and soluseptazine were ineffectual, but good results were obtained clinically by Hannah and Hobson<sup>32</sup> in nine cases with a mortality of 22 per cent. Pujol and Gunchon<sup>33</sup> treated one patient, with recovery, and Winchester<sup>34</sup> reported two cases of recovery. Whitby<sup>3</sup> found sulfapyridine as active (or more active) against meningococci in mice as sulfanilamide, and Hobson and MacQuade<sup>35</sup> have treated six patients without a death.

Rosenthal and Bauer<sup>36</sup> found that disulfanilamide (0.5 gm per kilo) in mice protected 90 per cent, while the same dose of sulfanilamide protected only 70 per cent, prontosil, neoprontosil and other derivatives were less effective. They used the disulfanilamide (sulfanyl-sulfanilamide) suspended in oil subcutaneously and, as pointed out by Long and Bliss,<sup>42</sup> differences in solubility, absorption and excretion have not been considered in these tests. Feinstone, Bliss and Long<sup>37</sup> state that sulfanilamide, disulfanilamide, diamino-diphenyl sulfone and di(acetylamino) diphenyl sulfone, all showed the same degree of therapeutic activity against the meningococcus, but that from all points of view sulfanilamide is the most suitable compound for the treatment of streptococcal and meningococcal infections.

Marshall, Emerson and Cutting<sup>38</sup> have shown that rapid absorption (in four to five hours) of sulfanilamide occurs from the gastro-intestinal canal and rapid passage into the spinal fluid to levels only slightly below that of the blood. Prontosil or neoprontosil is less rapidly utilized. They noted even bet-

ter concentration in the blood from oral therapy than from subcutaneous therapy, and under usual conditions there seems no advantage in administering the drug by any route other than the mouth. Retan<sup>39</sup> reported in monkeys that intravenous hypotonic salt solution after the administration of sulfanilamide will increase the relative concentration of the drug in the spinal fluid, but Allot<sup>40</sup> has shown that the spinal fluid level rises rapidly with continued administration of sulfanilamide and the relative concentration increases after the first few hours.

As the drug is rapidly excreted, the interval of dosage should be short (four hours) to maintain a uniformly high level. The fluid intake may be normal but, if too high, the more rapid elimination by the kidneys will reduce the blood level.

TABLE 5

RECURRENCES AFTER TREATMENT WITH SULFANILAMIDE OR ALLIED CHEMICALS

Author	Duration of therapy	Interval after end of therapy to relapse	Drug	Route.
Eldahl	5 days	8 days	Sulfanilamide	Intrathecally and subcutaneously
Willien	2 and 3 days with 2 day interval	12 days	Sulfanilamide	Intrathecally and subcutaneously
Hobson and MacQuade	19 days	29 days	Sulfapyridine	Mouth
Waghelstein	No details	given	Not sulfanilamide	

In much of the experimental work a single or a few doses have been used and, as the evidence points to therapeutic efficiency being obtained by a continued high level, it is possible that some of the lack of agreement in experimental and clinical studies is due to this fact. It seems certain that not only must an adequate concentration be reached in the fluids, but that this must be maintained for some few days after the effect appears. There is great variation under the same dosage in the concentration, depending partly on absorption and chiefly, apparently, on elimination through the kidneys. This irregularity is greater with sulfapyridine.

Recurrences or relapses have been reported by Willien,<sup>21</sup> Eldahl,<sup>20</sup> Waghelstein,<sup>19</sup> and by Hobson and MacQuade<sup>30</sup> (Table 5). Apparently recurrence is more apt to occur when the concentration is too low and is not continued for some days.

Long and Bliss<sup>41</sup> have recommended the following dosage

Size of patient.	Initial dose.	Subsequent dosage
100 pounds	50-80 grains	15 grains every 4 hours
50-90 pounds	30-50 grains	10-15 grains every 4 hours
25-50 pounds	20-30 grains	5-10 grains every 4 hours

Effective levels in the blood may be as low as 4 to 5 mg per 100 c.c., but the optimum is 10 mg or more and, in the spinal fluid, at least half that.

The duration of therapy in this series, because of the fear or uncertainty of recurrence, was about two weeks and even up to three weeks or more. It is probable that such prolonged treatment is unnecessary and that the period can be reduced to seven to ten days if good concentrations are maintained.

Long and Bliss<sup>42</sup> advise that a concentration of the drug at about 15 mg per 100 c.c. in the blood and 10 to 12 mg per 100 c.c. in the spinal fluid should be maintained until signs of infection and bacteria have disappeared for three days and then tapering off the therapy until the patient is up and about.

Our policy in future cases will be to continue therapy for at least three days after clinical and bacteriologic clearing and then to reduce the dosage over the next seven days.

### CONCLUSIONS

- 1 Sulfanilamide and some related compounds are efficient in the treatment of meningococcus infections.
- 2 The oral route is as efficient, or more efficient, generally than other routes.
- 3 The dosage should be large enough to produce optimum levels in the blood and fluids rapidly, and should be continued possibly at lower levels for several days (seven to ten) after clinical subsidence.
- 4 Sulfanilamide is probably the most suitable of these compounds now available for treatment of meningococcic meningitis.
- 5 Less damage to the central nervous system occurs in



sulfanilamide oral therapy than in serum therapy intrathecally

6 Antimeningococcic serum may be of value combined with chemotherapy in some cases, but it is not usually required

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## CLINIC OF DRS WALTER BAUER AND HOWARD C COGGESHALL

FROM THE MEDICAL CLINIC OF THE MASSACHUSETTS GENERAL  
HOSPITAL, THE DEPARTMENT OF MEDICINE, HARVARD  
MEDICAL SCHOOL, AND THE MASSACHUSETTS DEPARTMENT  
OF PUBLIC HEALTH

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### THE TREATMENT OF GONOCOCCAL INFECTIONS WITH SULFANILAMIDE, SULFAPYRIDINE AND ALLIED COMPOUNDS\*

#### INTRODUCTORY REMARKS

THE advent of sulfanilamide has established beyond all doubt that effective chemotherapy against microbial disease is possible. The introduction of sulfanilamide as a therapeutic agent in the treatment of gonorrhea and its complications represents the greatest advance ever made in the treatment of this disease. It has proved to be fully as efficacious as its much heralded predecessor, fever therapy<sup>1</sup>. Its advantages over fever therapy are many<sup>1, 2</sup>. It is much less complicated, it does not require a special apparatus and a trained personnel. It is also a less heroic and less dangerous form of therapy. Most important of all it is relatively inexpensive and therefore is available for the treatment of all types of gonococcal infections.

If an orally administered form of therapy as inexpensive as sulfanilamide represents the greatest advance ever made in the treatment of gonococcal infections, all physicians should be thoroughly acquainted with the practical aspects of its administration. If such knowledge is made use of, the medical profession can reduce greatly the incidence of gonorrhea and

\*This is publication No. 35 of the Robert W. Lovett Memorial for the Study of Crippling Disease, Harvard Medical School.

The expenses of this investigation have been defrayed in part by a grant from the Commonwealth Fund.

its complications and the economic loss resulting therefrom. In the time allotted for this clinic, we shall attempt to discuss the many problems concerned with the treatment of gonococcal infections with sulfanilamide and its allied compounds as well as comment on the treatment of sulfanilamide-resistant gonococcal infections.

#### THE ADMINISTRATION OF SULFANILAMIDE

The dose of sulfanilamide administered and the regularity with which it is given are extremely important if one is to obtain the highest percentage of cures. Many are the cases labeled as "sulfanilamide failures" which represent improperly administered, inadequate doses of the drug and failure to keep the fluid intake constant. Therefore, considerable time will be devoted to this most important aspect of sulfanilamide therapy and to the toxic manifestations which may be encountered.

*In the treatment of patients with sulfanilamide, the desired blood level must be kept constant. This can be achieved only by administration of the drug every four hours, day and night, and maintaining a constant fluid intake.*

Observance of this simple rule is imperative because sulfanilamide is as readily excreted by the kidneys as it is absorbed by the gastro-intestinal tract<sup>3, 4</sup>. In most cases of gonococcal infection in which patients are receiving sulfanilamide, a total twenty-four-hour fluid intake of 2,000 c c is adequate. As might be inferred from the above, maintaining a *constant fluid intake* is more important than the amount allowed for any twenty-four-hour period, providing it is not excessive. An excessive intake of fluid results in an increased urinary output, which in turn reduces the blood sulfanilamide to a lower level than anticipated. In consequence of an excessive intake, a larger dose of the drug will be required to maintain the desired concentration of sulfanilamide in the blood.

We have employed large doses of sulfanilamide in the treatment of gonococcal infections, believing that this mode of administration insures the largest percentage of cures. The daily intake of fluid is usually maintained at 2,000 c c. The dose of sulfanilamide is calculated in the following manner:  $\frac{3}{4}$  grain

per pound of body weight, providing the total dose does not exceed 120 grains, or 8 gm. This calculated dose represents the amount to be given *every twenty-four hours*.

Knowing the calculated dose, the drug is then administered orally in one of two ways: (1) half the calculated dose is given initially and again in four hours, and then one-sixth of the calculated dose is given every four hours day and night, (2) one-sixth the calculated dose is given initially and every four hours. When the drug is given according to the first schedule, a blood sulfanilamide level of from 10 to 15+ mg per cent will result, whereas adherence to schedule 2 will allow for the maintenance of a blood sulfanilamide level of between 5 and 10 mg per cent. The dosage advocated by Long and Bliss<sup>14</sup> varies somewhat from that used by us and is given in Tables 1 and 2 below.

We well appreciate that sulfanilamide cures are experienced when the blood sulfanilamide level remains as low as 3 to 5 mg per cent throughout the period of therapy. It has been our experience, however, that more cures are obtained when the blood sulfanilamide level is maintained at 10 mg per cent or higher. This we believe is extremely important in the more serious gonococcal complications, such as an acute gonorrheal arthritis, which may go on to joint destruction. It is of

TABLE 1

THE AMOUNTS OF SULFANILAMIDE NECESSARY TO ESTABLISH BLOOD LEVELS OF 10 TO 15 MILLIGRAMS PER CENT\*

Weight of patient, pounds	Initial dose per os grams	Maintenance dose per os q 4 hours (day and night), grams	Total dose first 24 hours, grams per kilo
150	4.8	1.2	0.15
125	4.2	0.9	0.15
100	3.6	0.9	0.18
75	3.6	0.9	0.23
50	3.0	0.6	0.26
25	1.8	0.3	0.3

\*If the infection is mild or of moderate severity, the large amounts of sulfanilamide indicated in Table 1 are not needed and the doses of the drug as outlined in Table 2 will generally be sufficient to control the infection.<sup>14</sup>

\*Taken from Long, P. H., and Bliss, E. A. *The Clinical and Experimental Use of Sulfanilamide, Sulfapyridine and Allied Compounds*. By permission of The Macmillan Company, New York, publishers.

TABLE 2

THE AMOUNTS OF SULFANILAMIDE NECESSARY TO ESTABLISH BLOOD LEVELS OF 4 TO 8 MILLIGRAMS PER CENT\*

Weight of patient, pounds.	Calculated daily dose.		Dose per os q 4 hours (day and night), grams.
	Grams	Grams per kilo	
150	5 4	07	0 9
125	5 4	09	0 9
100	5 4	12	0 9
75	4 3	12	1 of 1 2† 5 of 0 6
50	3 6	16	0 6
25	1 8	16	0 3

\* Taken from Long, P H, and Bliss, E A. The Clinical and Experimental Use of Sulfanilamide, Sulfapyridine and Allied Compounds By permission of The Macmillan Company, New York, publishers

† One dose of 1 2 grams followed by 5 of 0 6 grams

equally great importance if we are to keep the incidence of gonococcal infections as low as possible

We have observed patients who experienced no improvement of their gonorrheal arthritis or genito-urinary infections following seven days of therapy with a constant blood sulfanilamide level of 7 5 mg per cent, who showed marked improvement forty-eight to seventy-two hours after a level of 10+ mg per cent was attained. However, this does not mean that high blood sulfanilamide levels will assure a favorable result. Blood sulfanilamide levels higher than 20 mg per cent are not indicated and are no more effective than levels between 10 and 20 mg per cent. This was well demonstrated in our failure to cure two patients with acute gonococcal urethritis even though the blood sulfanilamide levels were maintained between 35 and 40 mg per cent for as long as seven days.

Failure to obtain a cure should always lead one to suspect that the blood sulfanilamide has not been maintained at the desired level. This can be established only by direct determination. The determination of sulfanilamide and of certain allied compounds,<sup>5 6</sup> is a relatively simple procedure which is within the scope of any physician or well-trained technician. If therapy is controlled by doing blood sulfanilamide determinations regularly, the treatment will be more correctly administered. However, the ease and regularity with which a

constant level of sulfanilamide is maintained in the blood, providing the above simple rules are observed, makes possible a reasonable approximation of the desired blood concentration.

Failure to maintain a constant blood sulfanilamide level should lead one to suspect that the dosage is inadequate, that the drug has not been administered regularly (*every four hours, day and night*), or that the fluid intake has not been kept constant. Any one of these omissions is corrected readily.

Other workers<sup>7 8 9 10 11</sup> have employed much smaller doses of sulfanilamide than herein advocated. Until it has been definitely proved that as high a percentage of cures and as small a number of recurrences result with the administration of small doses of sulfanilamide, we are of the opinion that the larger doses should be employed. True, the administration of small doses allows one to treat ambulatory patients. However, one must admit that the number cured is smaller and the percentage developing complications and recurrences is higher. In addition there is suggestive evidence that when sulfanilamide is administered in doses too small to effect a cure, the resistance of the organisms to subsequent treatment with large doses may be increased.<sup>1</sup>

Patients receiving the larger doses of sulfanilamide *should not be ambulatory* because such doses are productive of a mild to moderate acidosis,<sup>1 12</sup> the symptoms of which are greatly enhanced if the patient is allowed normal activity. Because of the regularly recurring acidosis encountered in sulfanilamide therapy, certain workers<sup>13 14</sup> have advocated the administration of regular doses of sodium bicarbonate in amounts up to 3.6 gm per day. We observed the same average reduction of 10 volumes per cent of the serum carbon-dioxide combining power in patients receiving sodium bicarbonate as in those who did not. Therefore, we are of the opinion that the routine administration of sodium bicarbonate in the doses herein advocated does not begin to compensate for the alkali loss resulting from sulfanilamide therapy.<sup>15, 16</sup> Its administration is optional and not imperative. In some instances it does seem to reduce somewhat the associated nausea and vomiting.

Patients receiving full doses of sulfanilamide should be seen daily if possible. Their temperature, pulse and respirations should be recorded every four hours. Complete blood examinations should be made every third to seventh day.



Blood sulfanilamide determinations should be made, if possible, at the end of the first forty-eight hours of therapy and as often thereafter as is needed to assure the physician that the desired blood concentration has been attained and is being maintained

As Long<sup>14</sup> has aptly stated "The only contraindication to treatment with sulfanilamide is the history that the patient had taken the drug on a previous occasion and had suffered a severe reaction In such an instance we would hesitate, and would administer the drug only with the greatest of care, following the patient's course conscientiously"\* Previously existing anemias and low leukocyte counts of themselves are not contraindications to therapy A diet consistent with the severity and type of infection and the patient's desires is allowed Other drug therapy, such as morphine, codeine, salicylates, barbiturates, ferrous sulfate, digitalis, arsphenamine, pantopon, etc., are permitted The bowels are readily controlled with cascara, mineral oil and enemas Transfusions are employed if correction of an existing anemia is necessary in order to continue treatment Surgery, although rarely indicated in acute gonococcal infections, could be undertaken

Parenteral administration of sulfanilamide is very rarely indicated in acute gonococcal infections because, except for the rare case of pelvic peritonitis, endocarditis, acute arthritis, or meningitis, it is well tolerated by mouth This is fortunate because it is practically impossible to maintain a constant blood sulfanilamide level when the drug is administered other than orally

Administration of the drug should be continued until one has satisfied the most rigid definitions of a cure In most cases of gonococcal infection, marked improvement is noted within from forty-eight to seventy-two hours If such is not noted the dose of the drug should be increased If one fails to obtain evidence of improvement within another seventy-two-hour period, the dose should be increased, if necessary, until a blood sulfanilamide level of 20 mg per cent is obtained In those instances where improvement is noted within seventy-two hours, the full dose should be continued for a total of seven days, and then the dose can be reduced one-third or

\* Long, P H and Bliss, E A. *The Clinical and Experimental Use of Sulfanilamide Sulfapyridine and Allied Compounds* By permission of The Macmillan Company, New York, publishers

are mild and of no importance while others are severe and may endanger the life of the patient \*\*

**Cyanosis**—Varying degrees of cyanosis are observed in all patients receiving large doses of sulfanilamide. It is not an alarming symptom and can usually be disregarded. It is usually apparent within the first twenty-four hours after the drug is instituted and disappears rapidly after it is discontinued. It has been ascribed as being due to (1) sulfhemoglobinemia,<sup>18</sup> (2) methemoglobinemia,<sup>19</sup> (3) staining of the erythrocytes by a pigment formed from sulfanilamide.<sup>20</sup> Further work is necessary before the exact cause of the cyanosis can be stated. If an appreciable amount of methemoglobin is demonstrable,

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methemoglobinemia in such instances can be controlled by the oral or intravenous administration of methylene blue

**Acidosis**—As stated previously, a reduction of the serum carbon-dioxide combining power is frequently observed in patients receiving sulfanilamide. The reduction encountered is frequently very slight, yet in every instance premedication values were higher than those obtained during therapy.<sup>1</sup> The lowest serum carbon-dioxide combining power we have observed was 41 volumes per cent.<sup>1</sup> The average reduction was 10 volumes per cent. This reduction of carbon-dioxide combining power occurred even though the patients received amounts of sodium bicarbonate equal to the sulfanilamide dosage.

Observations in this laboratory allow us to conclude that sulfanilamide produces a primary alkali-deficit type of acidosis<sup>15, 16</sup>. This particular toxic manifestation is rarely of serious consequence. It can be relieved by large oral doses of sodium bicarbonate, or sodium racemic lactate. When parenteral therapy is indicated, a  $\frac{1}{2}$  molar solution of sodium racemic lactate is the medication of choice.

**Fever**—Occurrence of fever during sulfanilamide therapy has been reported by many investigators.<sup>1, 13, 14, 21</sup> In one series of cases it occurred in 15.6 per cent of the patients.<sup>21</sup> It usually appears between the seventh and tenth days of sulfanilamide therapy. It has been noted earlier, and in some instances as late as the fourteenth day.<sup>21</sup>

The onset is usually abrupt and has on occasions appeared despite the discontinuation of sulfanilamide. Such febrile reactions represent a specific reaction to the drug. Therefore, the persistence of fever without clinical evidence of infection should always lead one to suspect that it is due to sulfanilamide. If such is the case, omission of the drug should result in subsidence of the fever. One should realize that fever is often the forerunner of a more serious toxic manifestation of sulfanilamide therapy such as acute hemolytic anemia, agranulocytosis, and hepatitis. This being the case, it is obvious that fever constitutes the one most important warning signal and should be heeded accordingly.

**Anemia**—Severe hemolytic anemias, such as have been reported,<sup>22, 23</sup> usually occur on the third to fifth day of treatment. As stated above, fever frequently precedes the onset of

such anemias Careful hematologic studies<sup>1</sup> have revealed that sulfanilamide therapy in addition frequently causes a slow, progressive, subclinical hemolytic anemia

The mechanism of the production of such anemias is unknown That they do not represent a true idiosyncrasy has been proved<sup>24</sup> Because this slow, progressive type of hemolytic anemia develops in such a large percentage of patients receiving large doses of sulfanilamide, frequent blood examinations should be made during and following the period of therapy Patients with severe anemias who require sulfanilamide treatment should be transfused prior to and coincident with the administration of the drug If severe anemias occur, the drug should be discontinued and the patient transfused The subclinical hemolytic anemia, unless unusually severe, does not require any special therapy In fact patients receiving treatment other than transfusions respond no more rapidly than do the untreated ones This type of anemia is not necessarily related to the amount of sulfanilamide administered nor to the length of time it is given In some cases leukocytosis develops subsequent to the administration of the drug We have observed leukocytoses of this type, in one instance reaching 30,000

**Leukopenia**—Mild to moderate leukopenia is occasionally observed during sulfanilamide therapy<sup>1</sup> In one patient, a leukopenia of 1800 was observed twenty-two days after discontinuance of the drug, whereas in another the leukocyte count fell to 2800 on the twenty-fifth day of therapy<sup>1</sup> The percentage of polymorphonuclear leukocytes never fell below 43 per cent. In these two instances the leukocyte counts returned to normal in a few days without the employment of any of the so-called specific forms of therapy Here, as in the case of the anemia, there was no relation to the amount of the drug given or to the length of time it was administered The exact mechanism responsible for such a leukopenia is as yet unknown That it is not the same type as results from amidopyrine is suggested by the fact that readministration of the drug to such patients following a return of the leukocytes to normal does not necessarily result in reproduction of the leukopenia.<sup>25</sup>

**Agranulocytosis**—The occurrence of agranulocytosis as well as leukopenia following sulfanilamide therapy has been

reported by various workers<sup>24, 25, 26</sup> In some of the reported cases severe infection may have been a predisposing factor In some instances death has occurred One patient is reported to have made a spontaneous recovery following the development of agranulocytosis<sup>27</sup>

If this complication should appear, the drug should be discontinued, and fluids forced, if necessary by the intravenous route There is little evidence that pentnucleotide or nucleotide preparations are of value in treating this type of agranulocytosis Transfusions are not indicated unless the hemoglobin is markedly reduced

It is interesting that sulfanilamide has been employed to combat the sepsis complicating amidopyrine agranulocytosis<sup>14</sup> In fact, Long<sup>14</sup> advises that in cases in which patients are suffering from agranulocytosis and streptococcal sepsis, these drugs are not only indicated but may be life-saving

The occurrence of leukopenia and agranulocytosis during the administration of sulfanilamide suggests the necessity for frequent leukocyte and differential counts during and following the administration of this drug

**Skin Reactions**—The most frequently encountered skin reaction is a morbilliform eruption, although many other types have been encountered<sup>21 24</sup> Such rashes are associated with fever The most common complication to develop following the appearance of fever is some type of skin eruption Severe exfoliative dermatitis has been encountered during sulfanilamide therapy<sup>14</sup> In certain instances erythredema has been observed following exposure to sunshine In such instances the rash has been limited to the exposed surfaces of the skin In one of our cases this reaction disappeared five days later, even though the dosage of sulfanilamide remained unchanged<sup>1</sup> Previous reports have called attention to similar skin reactions following exposure to sunlight Because of this risk, it would seem unwise to allow patients receiving sulfanilamide to expose themselves to the direct rays of the sun

Such skin manifestations do not represent serious complications, and require no treatment other than discontinuance of the drug The one exception to this rule is when continuation of the therapy represents a matter of life or death Sulfanilamide can be readministered to patients who have previously suffered from skin lesions, providing it is administered

cautiously at the onset<sup>1 14</sup> The manner of production of such sulfanilamide skin lesions is as yet not understood

**Hepatitis**—The occurrence of hepatitis as a toxic manifestation of sulfanilamide therapy has been reported by several workers<sup>14</sup> Such hepatitis may be fatal and, at autopsy, the liver shows the classical gross and microscopic findings of acute yellow atrophy If this complication should arise, the drug should be discontinued, fluids forced, and a high carbohydrate intake prescribed

#### MODE OF ACTION OF SULFANILAMIDE

The exact mode of action of sulfanilamide in bacterial infections has not been established Certain workers have suggested that sulfanilamide therapy may be more effective in individuals with gonococcal infections who possess a partial degree of immunity, as measured by the bacteriocidal power of the serum and the presence of a positive gonococcal complement-fixation test

This type of evidence is indirect and does not allow one to draw any conclusions We have observed cures in patients with proved gonorrheal arthritis whose complement-fixation tests were negative and never did become positive There is no doubt but that a clearer understanding of the successes and failures in the treatment of gonorrhea with sulfanilamide would be obtained if we possessed a better knowledge of the antibodies in the various stages of infection Further studies of this type must be undertaken That sulfanilamide when administered in large doses has a specific effect on the gonococcus has been well demonstrated

#### CLINICAL RESULTS IN THE TREATMENT OF GONOCOCCAL INFECTIONS WITH SULFANILAMIDE

When the clinical diagnosis of gonorrhea or one of its complications is made, every effort should be exerted to corroborate the diagnosis, if possible, by laboratory tests The best method available is the demonstration of gonococci by cultural methods Demonstration of the organism by direct smear is probably correct in most instances, but is not positive as often as cultures The gonococcal complement-fixation test should never be relied upon other than as corroborative or suggestive diagnostic evidence

In both the male and the female, at least three attempts should be made to demonstrate the presence of gonococci. In the case of the male, this means obtaining smears and cultures from the urethral and prostatic fluid on at least three successive occasions. In the female, smears and cultures should be obtained from the vagina, cervix, and from Bartholin's and Skene's glands on three successive occasions. These are much more apt to be positive prior to, during, or immediately following menstruation.

One should exercise great caution before pronouncing a patient cured of gonorrhea or one of its complications following the administration of sulfanilamide. If such caution is not employed, many individuals who are asymptomatic carriers will consider themselves well and in consequence will be responsible for an increasing incidence of gonorrhea in their respective communities. The criteria of cure of gonorrhea have been very adequately presented by Pelouze.<sup>28</sup> This article should be consulted by all those who treat any number of patients suffering from gonorrhea.

**Vulvovaginitis**—From the reports to date concerning the use of sulfanilamide in the treatment of gonococcal vulvovaginitis in infants and children,<sup>14</sup> one is forced to conclude that sulfanilamide therapy is not the method of choice. The results on the whole have been disappointing and discouraging. We do not advocate it.

**Gonorrheal Ophthalmia**—The results obtained in the treatment of gonorrheal ophthalmia have been much more encouraging.<sup>14</sup> The results to date would suggest that the drug is of considerable value in the treatment of this particular complication. We advocate doses such as are herein prescribed.

**Uncomplicated Gonorrhea**—Uncomplicated gonorrhea in the male and in the female responds extremely well to sulfanilamide therapy. The results in some instances have been as high as 80 to 90 per cent cured. Because cures have frequently been obtained on small doses of sulfanilamide, various workers are of the belief that a concentration of 5 mg per cent is sufficient. We, however, are of the opinion that a larger percentage of cures will be obtained if larger doses of sulfanilamide are administered.

Curing acute gonorrhea as soon as possible is extremely important. The sooner the cure, the less likely one is to en-

counter the more common complications, such as prostatitis, epididymitis, Bartholinitis, Skenitis, salpingitis, peritonitis and arthritis. Because of our experience, we cannot agree with other workers, namely, that more cures are observed in those cases in which patients are treated in the second or third week of the gonococcal infection.

### GONORRHEAL COMPLICATIONS

It has been the experience of many workers that the common complications of acute gonococcal urethritis and cervicitis respond fully as well to sulfanilamide as does uncomplicated gonorrhea. Pregnancy is not a contraindication to sulfanilamide therapy.<sup>1 14</sup> Whether local therapy should be used in conjunction with sulfanilamide has, to date, not been accurately determined. Certain workers favor such combined therapy over treatment with sulfanilamide alone. There can be no objection to such combination therapy if used intelligently. There is no justification for combining gonococcal vaccine therapy with sulfanilamide in the treatment of any type of gonococcal infection. Unless there exists some contraindication, we advocate the limiting of fluids to 2,000 c.c. per day in acute gonorrhea, with or without complications.

**Gonococcal Meningitis and Endocarditis**—We have had no experience in the treatment of either of these types of gonococcal infections. Long and Bliss<sup>14</sup> report two cases of gonococcal endocarditis in which the endocarditis and the bacteremic phase of the disease were brought under control when sulfanilamide was administered in doses as set forth in their Table 1. "Both of these patients developed signs of acute nephritis during the course of their infection. In one individual, this complication eventually proved fatal. In this type of gonorrheal infection, prolonged therapy is indicated in order that recurrences of the infection may be avoided."\* Long also refers to two reports concerning the use of sulfanilamide in gonococcal meningitis.<sup>14</sup>

**Gonorrheal Arthritis**—Arthritis is a common and severe complication of gonorrhea. In the past, gonorrheal arthritis has caused joint destruction and disability in approximately

\* Long, P. H. and Bliss, E. A. *The Clinical and Experimental Use of Sulfanilamide, Sulfapyridine and Allied Compounds*. By permission of The Macmillan Company, New York, publishers.



25 per cent of the cases. Such joint disabilities represent intra-articular destruction and periarticular fibrosis in consequence of inflammation resulting from the invasion of such tissues by gonococci.

Experience with sulfanilamide therapy has taught us that such disabilities should rarely if ever occur in the future, providing the correct diagnosis is made early and the drug is administered in large doses as soon thereafter as is possible. This fortunate state of affairs is due to the fact that gonococci within the joint cavity are seemingly much more susceptible to sulfanilamide therapy than are the same organisms in the genito-urinary focus. This probably signifies that the genito-urinary tract is a more favorable habitat for the gonococcus than is the joint cavity. It is not unusual in our experience to cure the patient's gonorrheal arthritis and have the genito-urinary focus persist. However, this occurs less frequently with sulfanilamide therapy than with fever therapy.

The incidence of gonorrheal arthritis and the subsequent disability can be greatly reduced if all cases of uncomplicated gonorrhea are adequately treated with sulfanilamide as soon as possible.

Cases of proved gonorrheal arthritis with organisms in the joint respond more dramatically and promptly to sulfanilamide than do those cases in which the organisms are not demonstrable. This again is most fortunate because it is the former type which is responsible for the severe joint destruction encountered.

From our experience it is apparent that, with large doses of sulfanilamide, marked clinical improvement can occur as early as within forty-eight to seventy-two hours. Corroborative laboratory evidence of this improvement is obtained from repeated synovial fluid analyses. Such analyses reveal that the infected fluid may become sterile within forty-eight hours. With sterilization of the fluid, the cytological abnormalities may be restored to practically normal limits within seven days. The rapid restoration of the joint to normal in those cases in which the roentgenograms are negative serves to emphasize the wisdom of early treatment with large doses of sulfanilamide. In those cases where roentgenograms show evidence of joint destruction prior to the administration of therapy, the same marked clinical improvement and sterilization of the synovial

fluid is noted when large doses of the drug are given. Repeated roentgenograms in such instances show that destruction of the joint is arrested and recalcification of the subchondral bone made possible. In this type of case the final end-result is directly dependent upon the extent of the joint destruction prior to the onset of therapy.

The results obtained in treating proved gonorrheal arthritis without organisms in the joints are in most instances fully as satisfactory as in those with infected fluids. In this group we encountered a number of patients who did not respond until their blood sulfanilamide levels were increased to 10 mg per cent or higher. Failure to obtain marked relief until such blood sulfanilamide levels had been obtained is one of our reasons for believing that the larger doses of sulfanilamide will give the most rapid improvement and the largest percentages of cures. Those patients who had previously received small doses of sulfanilamide responded more slowly, suggesting that sulfanilamide administered in doses too small to effect a cure may increase the resistance of the organism.

Patients with probable gonorrheal arthritis respond fully as well as do those with proved cases. In such instances the response to therapy is of diagnostic significance. Such therapeutic tests should always be employed in any case of arthritis which might possibly be due to the gonococcus.

Improvement of chronic gonorrheal arthritis of six to twelve weeks' duration with sulfanilamide therapy is never dramatic. It would seem unreasonable to expect prompt and complete subsidence of soft tissue inflammatory changes, removal of fibrosed tissue and restoration of destroyed joint surfaces encountered in such cases. It is sufficiently amazing to witness the restoration to normal of a case of severe acute gonorrheal arthritis so promptly following the administration of sulfanilamide. Our results suggest the importance of early treatment with large doses in order to obtain the highest percentage of cures.

The sedimentation rate falls rapidly in those cases of gonorrheal arthritis showing striking improvement, whereas patients improving slowly exhibit a corresponding slower fall in the sedimentation rate. Thus it would appear that a rapid fall in the sedimentation rate is indicative of a satisfactory response to the dose of sulfanilamide being administered. If the

rate remains unchanged, it should suggest inadequate dosage, an incorrect diagnosis, or a resistant gonococcal strain

The gonococcal complement-fixation test may fail to become positive in those patients with gonorrheal complications if treatment is started while it is still negative, indicating that the patients are cured before sufficient antigen is absorbed. It further suggests that a partial immunity, as indicated by a positive complement-fixation test, is not a prerequisite to curing a gonococcal infection with sulfanilamide. In about 50 per cent of the cases, it becomes negative within two months from the time therapy is instituted. Following fever therapy, the complement-fixation test does not become negative in such a large percentage of the cases within this same time interval.

From our clinical results with sulfanilamide in the treatment of patients with rheumatoid arthritis, it seems fair to conclude that sulfanilamide therapy does not exert any specific effect on the agent causing this disease, nor does it influence its course. The sedimentation rates were likewise uninfluenced. As stated before, sulfanilamide therapy may be of diagnostic aid in an occasional case of arthritis when the etiology is in question.

**Sulfanilamide-resistant Gonococcal Strains**—There can be no doubt that a small percentage of gonococcal infections are not cured even though large doses of sulfanilamide, as herein advocated, are employed for as long as three to four weeks. Whether such failures represent sulfanilamide-resistant gonococcal strains or failure of some inherent host factor to play its usual rôle is unknown. There is partial evidence favoring both theories. There is reason to believe that previous small doses, insufficient to cure the gonococcal infection, may increase the resistance of the organism to subsequent large doses of sulfanilamide<sup>1</sup>. Further studies will be required before any of these questions can be answered.

Those patients who fail to respond to large doses of sulfanilamide can subsequently be treated in one of a number of ways. One can resort to fever therapy, a combination of fever therapy and sulfanilamide, sulfapyridine, or sulfanilyl sulfanilamide.

Our present working rule is to try sulfapyridine in cases of "sulfanilamide failure". If this fails one can then employ fever therapy with or without sulfanilamide. Our experience

to date with such failures has been so limited that we are not in a position to speak concerning the advantages of one form of therapy as compared to the other

In the occasional patient with a residual genito-urinary focus that we encounter following the administration of large doses of sulfanilamide, we have had recourse to local therapy, using, in most instances, 10 per cent neosilvol urethral instillations, three times a day. When indicated, prostatic massage has been employed in conjunction with such local therapy. In those cases in which it takes weeks and months to obtain a cure, it is always difficult to know whether to ascribe it to the therapy employed or to look upon it as a natural cure

The available data pertaining to the treatment of uncomplicated gonorrhea do not prove that there is any merit in the combined therapy over treatment with sulfanilamide alone. Further studies will eventually establish whether the combination of local treatment and the drug are advantageous. Certainly there is no contraindication to such combined therapy.

**Sulfapyridine, Sulfanilyl Sulfanilamide, and Allied Compounds**—In speaking of sulfapyridine Long<sup>14</sup> very aptly states "It is perhaps unfortunate that this drug has popped out of the box into the arena of controversy before the merits of sulfanilamide and the sulfanilyl sulfanilamides in the therapy of gonorrhea have been established, because it adds another unknown to an already difficult equation"\*

There can be little doubt concerning the efficacy of sulfapyridine in the treatment of gonorrhea and its complications. Only the passage of time and well-controlled studies will prove that it is or is not more efficacious than sulfanilamide. The greatest disadvantage to the use of sulfapyridine at the moment is the great frequency with which it causes the toxic symptoms of severe nausea and vomiting. This fact, plus the increased cost of sulfapyridine, are adequate reasons to continue to treat gonococcal infections with sulfanilamide until such time as it has been definitely proved that sulfapyridine is a far more effective chemotherapeutic agent. Our present regimen is to treat all gonococcal infections with large doses of sulfanilamide, in case of failure with this drug, we then

\* Long P. H. and Bliss, E. A. *The Clinical and Experimental Use of Sulfanilamide, Sulfapyridine and Allied Compounds*. By permission of The Macmillan Company, New York, publishers

employ sulfapyridine or sulfanilyl sulfanilamide. Adherence to this regimen will eventually enable us to establish the relative merits of these drugs and finally settle the existing controversies.

We have had no personal experience with the use of either sulfanilyl sulfanilamide or sulfanilyl dimethyl sulfanilamide in the treatment of gonococcal infections. The occurrence of peripheral neuritis as one of the toxic manifestations of sulfanilyl sulfanilamide is another reason for continuing with sulfanilamide in the treatment of gonococcal infections until the superiority of its allied compounds has been established. For further details pertaining to therapeutic claims, toxic effects and relative merits of these allied compounds, the reader is referred to Long's book, "The Clinical and Experimental Use of Sulfanilamide, Sulfapyridine and Allied Compounds."

#### SUMMARY

The specific value of any therapeutic measure can be established only if one is able to demonstrate that the clinical course of the disease is strikingly altered in a large percentage of cases. The results with sulfanilamide therapy indicate clearly the effects of this drug on gonococcal infections.

We have never observed such prompt arrest and subsidence of gonococcal infections to take place so regularly with other therapeutic measures, including fever therapy. The quick response of active gonorrheal arthritis is of itself sufficient to allow one to conclude that sulfanilamide exerts a specific chemotherapeutic effect on the gonococcus.

The allied compounds of sulfanilamide have not been demonstrated to be superior to sulfanilamide in the treatment of gonococcal infections. This coupled with the relative expense and increased toxic manifestations experienced by the patients are adequate reasons for sulfanilamide remaining the drug of choice. However, we do not advocate the administration of sulfapyridine and sulfanilyl sulfanilamide in those cases in which large doses of sulfanilamide have failed to cure the gonococcal infection.

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THE TREATMENT OF UNDULANT FEVER WITH  
SULFANILAMIDE AND RELATED COMPOUNDS

In the past two and a half years over thirty reports have appeared describing the effectiveness of sulfanilamide (para-aminobenzenesulfonamide) and related compounds in the treatment of undulant fever. These studies were prompted by the lack of a uniformly satisfactory therapeutic agent in this disease, in which the protracted fever, tendency to relapse, and the debilitating effects are so well known. During late 1936 and 1937, eight reports (<sup>1-8</sup> incl) appeared, chiefly from France and Germany, describing a total of ten cases of brucellosis successfully treated with sulfanilamide or related compounds. During 1938 and 1939, twenty-three more reports appeared (<sup>9-31</sup> incl), principally from America, England and Canada. Since the disease is relatively unusual, each author described only one case or a small series of cases. The case reports in the literature which have come to our attention to date (May, 1939) number seventy-four (Table 1).

A review of the published findings gives evidence that sulfanilamide is a valuable therapeutic agent in brucellosis. The statements of the present report are based on information gained from this review and from observations in a case of undulant fever treated by one of us (Blumgart) eighteen months ago<sup>17</sup> and observed to date. A report of this case is given to illustrate the effects of sulfanilamide therapy.



TABLE 1

TREATMENT OF UNDULANT FEVER WITH SULFANILAMIDE AND RELATED COMPOUNDS  
RÉSUMÉ OF RESULTS IN LITERATURE

Author	Number of cases treated	Number of recoveries	Number of failures	Number of cases showing relapse after recovery
Ahringsmann <sup>8</sup>	2	2	0	0
Bartels <sup>29</sup>	1	1	0	0
Berger <sup>2</sup>	1	1	0	0
Béthoux <i>et al</i> <sup>5</sup>	1	1	0	0
Béthoux <i>et al</i> <sup>7</sup>	1	1	0	0
Bevan <sup>8</sup>	1	1	0	1
Blumgart <sup>17</sup>	1	1	0	0
Bynum <sup>21</sup>	5	3	2	3
Francis <sup>11</sup>	2	2	0	0
Fraser <i>et al</i> <sup>21</sup>	2	2	0	0
Gaffney <sup>20</sup>	5	5	0	3
Grouès <sup>1</sup>	2	2	0	0
Haden <sup>27</sup>	1	1	0	0
Hall <i>et al</i> <sup>14</sup>	1	1	0	0
Livingston <sup>28</sup>	1	1	0	0
Lloyd <sup>9</sup>	1	1	0	0
Manson-Bahr <sup>12</sup>	3	3	0	2
Matthews <sup>22</sup>	1	1	0	0
Neumann <sup>25</sup>	20	16	4	2
Page <sup>23</sup>	1	1	0	0
Petzetakis <sup>18</sup>	1	1	0	0
Punch <sup>19</sup>	1	1	0	0
Richardson <sup>10</sup>	2	2	0	1
Sheppe <sup>16</sup>	1	1	0	0
Stern <i>et al</i> <sup>12</sup>	3	3	0	0
Suchier <sup>4</sup>	1	1	0	0
Thévenet <sup>2</sup>	1	1	0	0
Thomson <sup>26</sup>	3	3	0	1
Toone <i>et al</i> <sup>26</sup>	1	1	0	0
Traut <i>et al</i> <sup>24</sup>	2	2	0	0
Welch <i>et al</i> <sup>15</sup>	5	5	0	1
Total	74	68	6	14

## ILLUSTRATIVE CASE

A man, aged thirty-three, a meat packer, felt perfectly well until three weeks before admission when he experienced malaise, anorexia and fever ranging from 99° to 102° F. On several occasions he experienced chills and profuse perspiration and he suffered from increasing weakness.

On physical examination the patient appeared exhausted, torpid and flushed, but in no apparent pain. The examination was otherwise negative except for enlargement of the spleen, which was tender and palpable 2 cm below the costal margin. The spleen was smooth and firm in consistency. The body weight was 120 pounds. The temperature on admission was 103° F, heart rate 84 per minute, and respirations 20 per minute. Examination of

the urine was negative. The red cell count and hemoglobin percentage were normal. The white cells numbered 5,900 per cubic millimeter, of which 52 per cent were polymorphonuclear cells (with 7 band forms), 41 per cent lymphocytes, 4 per cent large mononuclear cells, and 3 per cent eosinophils. The heterophile agglutination test was negative, as were the agglutination tests for typhoid and paratyphoid A and B infections. Cultures of the stool and urine failed to yield any pathogenic organisms. The agglutination test for undulant fever was positive in a dilution of 1:3,600. During the first week of his stay in the hospital the patient showed increasing prostration, and temperatures were as shown in the chart (Fig 76). Three blood cultures taken during this time showed the presence of *Brucella abortus*\*. Organisms obtained from the cultures were later agglutinated by the patient's serum.

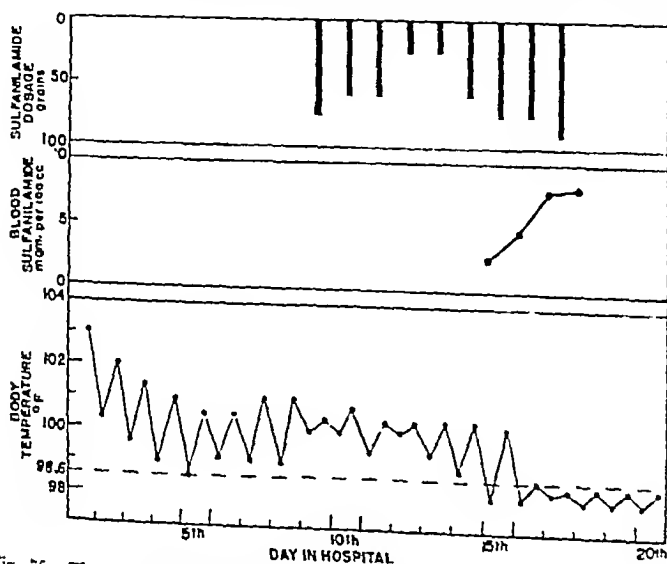


Fig 76—The dosage of sulfanilamide, amount of free sulfanilamide in the blood and the temperature curve, in Case I

On the ninth day in the hospital sulfanilamide therapy was instituted, 75 grains (5 gm) being given orally in six divided doses, as shown in the accompanying chart (Fig 76). A daily dose of 60 grains (4 gm) in divided doses was given on the tenth and eleventh days. The skin and mucous membranes appeared somewhat bluish and the patient was slightly nauseated. On the two succeeding days, the daily dosage was reduced to 25 grains (1.6 gm). The nausea disappeared. A fourth blood culture on the thirteenth day was positive for *Brucella* organisms. Since the clinical course had not been affected the drug was continued in increased dosage. On the fourteenth day

\* Throughout this communication the term "*Brucella abortus*" is used, although the necessarily detailed tests to differentiate between the different *Brucella* organisms were not made.

60 grains, and on the fifteenth day 75 grains, of sulfanilamide were given. The patient's temperature was not influenced, but he noted subjective improvement. The dosage on the sixteenth day was maintained at 75 grains despite marked bluish discoloration of the skin and mucous membranes, spectroscopic examination of the blood revealed no sulfhemoglobin. The temperature remained normal on this day, and the patient showed further clinical improvement. The concentration of free sulfanilamide in the blood was 7.7 mg per 100 c.c. Ninety grains (6 gm) of the drug were given on the seventeenth day. The temperature continued to remain normal and the concentration of free sulfanilamide in the blood was 8 mg per 100 c.c. During these last four days the patient did not experience gastro-intestinal distress. Sulfanilamide therapy was discontinued, the temperature remained normal, and the patient improved rapidly. He was discharged from the hospital four days later. The cyanosis due to sulfanilamide had completely disappeared within two days of cessation of medication. A blood culture taken two days before the patient was discharged from the hospital was negative for *Brucella abortus*. The red cell count and hemoglobin concentration were normal throughout the treatment. The white cell count was normal.

In the eighteen months since his discharge from the hospital the patient has experienced no fever or other symptoms of undulant fever, has been at work and feels entirely well. Physical examination six months after treatment was negative except for the spleen, the non-tender edge of which was palpable just below the left costal margin. Examination of the blood and urine was negative except for the persistence of a positive agglutination reaction for undulant fever through a dilution of 1:1,200. Physical examination eighteen months after treatment was entirely negative, the spleen was no longer palpable. The agglutination reaction for undulant fever at this time was negative through dilutions of 1:15 to 1:32,000.

#### REVIEW OF RESULTS IN ALL REPORTED CASES OF BRUCELLOSIS TREATED WITH SULFANILAMIDE AND RELATED COMPOUNDS

Rapid recovery has occurred in sixty-eight of the seventy-four reported cases of brucellosis treated with sulfanilamide or related compounds. In a large percentage of these cases the symptoms of undulant fever had been present about a month before sulfanilamide therapy was instituted, in some, symptoms had been present only a week, in a few, for several months. Positive agglutination reactions for *Brucella abortus* or *Brucella melitensis* were reported obtained before treatment in all but six cases. In eleven cases blood cultures were examined before treatment, in nine of these the blood cultures were positive. The presence of a palpable spleen was frequently noted, and a palpable liver was occasionally noted.

The temperature usually became normal between the second and twelfth days of treatment with sulfanilamide, the

average time being six to seven days. Subjective improvement was noted either at the time of return of the temperature to normal or for a few days preceding this. In many instances the evening temperature decreased gradually, over a period of a week, to normal, in others, the drop to normal was sudden after several days of treatment.

The *agglutination titer* was decreased following treatment. In five instances in which positive blood cultures were obtained before treatment the blood was again cultured after treatment. In four of these cases the blood culture became negative, in one it remained positive a week after subsidence of fever.

Of the six *failures* in the seventy-four cases, four were reported by Neumann,<sup>23</sup> and in three of these, as pointed out by the author, the dosage of sulfanilamide was quite inadequate. One of Neumann's patients failed to recover with a dosage similar to that effecting recovery in sixteen other cases in his series. The remaining two failures were reported by Bynum<sup>31</sup>, the case reports in these instances did not reveal whether the temperature subsided during sulfanilamide therapy.

Of the sixty-eight cases showing recovery from symptoms and drop of temperature to normal with sulfanilamide therapy, fifty-four cases showed no *relapses*. Fourteen cases showed one relapse, in most of these cases the patients were reported to be not so ill during the relapse as in the first instance, and recovery ensued after a second course of a few days treatment with sulfanilamide. These relapses usually occurred within a few days to two weeks after the original subsidence of fever and symptoms. The occurrence of a second relapse has not been reported.

The duration of observation of the cases up to the time of the various reports has been from one month to twelve months following sulfanilamide treatment, usually from three to six months. The case reported by the author<sup>17</sup> has shown no recurrence of symptoms or fever to the present, eighteen months since treatment. It cannot be stated at present whether relapses may appear in some cases after an intermission of months.

The detailed tests necessary to differentiate the various *Brucella* organisms have not been made in the cases reported.

Usually the agglutination titer was determined for either Br abortus or Br melitensis. In a few instances titers were determined for both Br abortus and Br melitensis, in these cases the higher agglutination titers found for Br abortus indicate that this organism presumably was the infecting agent. Although from the case reports it appears probable that most of the patients were infected with Br abortus, some of the patients, especially in Europe, presumably were infected with Br melitensis. Experimental studies<sup>32</sup> indicate that sulfanilamide affects all three types of Brucella infection.

### EXPERIMENTAL STUDIES

*In vitro* studies have shown bacteriostatic and bactericidal effects of sulfanilamide on all three types of Brucella organisms<sup>11, 32, 33</sup>. In guinea-pigs infected with Br abortus and Br suis organisms, Chinn<sup>32</sup> found negative cultures of the spleen and liver following 100 mg of sulfanilamide daily for a month, treatment was started two days after inoculation of the animals. Wilson<sup>34</sup> found sterility of the tissues of guinea-pigs inoculated with Br abortus and given 400 mg of sulfanilamide daily for five weeks, this author began treatment six weeks after the inoculation. Welch, Wentworth and Mickle<sup>15</sup> observed in cases of human brucellosis and in guinea-pigs infected with Brucella abortus that treatment with sulfanilamide markedly increases the phagocytic action of the white blood cells for Brucella organisms. When sulfanilamide is given to individuals infected with other diseases and to normal guinea-pigs, there is no change in their opsonocytophagic activity for Brucella abortus. These authors<sup>15</sup> suggest that this difference in response be utilized as a diagnostic criterion in questionable cases of undulant fever.

### DOSAGE OF SULFANILAMIDE

The daily dosage of sulfanilamide and the duration of administration of this drug in undulant fever have varied rather widely in different clinics. Except in a very few instances the concentration of sulfanilamide in the blood has not been measured, so that the required information to base treatment on this criterion is not available.

In adult patients with brucellosis, subsidence of fever has occurred with total daily dosages of 2 to 3 gm (30 to 45 grains) of sulfanilamide. The authors and many other investigators, chiefly American, have utilized daily dosages of approximately 4 to 6 gm (60 to 90 grains) during the period of fever. Neumann<sup>25</sup> found the small dosage of 5 c c of pron-tosil administered intramuscularly every other day to be quite inadequate.

It appears from a study of the carefully presented case reports that fever disappears about as promptly with a daily dose of 2 to 3 gm as with a daily dose of 5 gm. Relapses, however, appear to occur less frequently when the higher dosages are utilized and when treatment is continued for a few days after subsidence of fever. In an attempt to avoid relapses several authors have given small doses of the drug intermittently for a period of a few days, one week, three weeks, and six weeks, or thereabouts, after the subsidence of fever.

On the basis of these findings it would seem advisable to use daily dosages of approximately  $\frac{1}{2}$  grain per pound (equivalent to 5 gm [75 grains] in the case of a 150 pound man), with a maximum of 6 gm, divided in four or six doses, or to maintain a blood concentration of free sulfanilamide of approximately 8 to 10 mg per cent during the period of fever. A large single dose of 3 gm in an adult at the beginning of treatment will raise the level of sulfanilamide in the blood quickly. Sodium bicarbonate in amounts of one-half of the dose of sulfanilamide is advised to prevent acidosis.<sup>35</sup>

When feasible, treatment should be continued for three to four days after the subsidence of fever. Further treatment in the ensuing weeks is not advised, if relapse does occur, sulfanilamide may be administered again. The usual precautions required during treatment of any infections with sulfanilamide must be exercised.

Since the average time of disappearance of fever is six to seven days, the total duration of sulfanilamide therapy on the above regimen will usually not be more than twelve days. The continuation of treatment with sulfanilamide for a few days after the patient becomes free of fever will not greatly inconvenience him, for continuation of rest and close medical care are required anyway.

## TOXIC MANIFESTATIONS OF SULFANILAMIDE

There are no toxic reactions due to sulfanilamide which are peculiar to patients with undulant fever. The same watchfulness should be exercised when sulfanilamide or related compounds are utilized in the treatment of cases of brucellosis as is required when the drug is administered in other diseases. As is well known, cyanosis and certain cerebral symptoms, such as nausea, headache, dizziness, and loss of ability to concentrate, occur rather frequently in patients receiving sulfanilamide<sup>36</sup>. For the most part the drug can be continued, when indicated, in spite of these milder toxic manifestations. Acidosis, usually mild, occurs occasionally and may be combated by oral administration of sodium bicarbonate. Occasionally, dermatitis develops and the drug should be withdrawn immediately, except in very rare instances<sup>35</sup>.

Acute hemolytic anemia occurred in 3 per cent of 335 patients treated for various infections with sulfanilamide at the Johns Hopkins Hospital<sup>36</sup>. This serious toxic manifestation is usually encountered within the first week of treatment<sup>35, 37</sup> and demands immediate discontinuance of the drug, forcing fluids, and transfusion. Agranulocytosis has been encountered occasionally and has caused death in several instances, this severe toxic manifestation has usually occurred fourteen days or more after the onset of treatment and, rarely, has occurred after the drug has been discontinued<sup>37</sup>. Here again the drug should be discontinued immediately, fluids forced, and transfusions and pentnucleotides administered. Simple drug fever occurs at times during sulfanilamide therapy. Since patients developing a dermatitis, acidosis, acute hemolytic anemia or agranulocytosis show an early febrile response, the appearance of unexplained fever constitutes sufficient reason for discontinuance of the drug.

Because of these toxic effects, the drug should never be administered to patients without most careful guidance and watchfulness. Daily measurements of hemoglobin and white blood counts are strongly advised<sup>35, 37</sup>. The dosage of sulfanilamide in patients with renal disease or marked dehydration is less in order to maintain the same concentration of the drug in the body, and must be decided on the basis of repeated blood chemical findings<sup>38</sup>.

Long and Bliss<sup>35</sup> and Keefer<sup>37</sup> have discussed recently the present knowledge concerning the toxic effects of sulfanilamide

Despite the occasional development of serious toxicity due to sulfanilamide, the drug, when administered properly, is not contraindicated in undulant fever where its therapeutic value appears great. Since agranulocytosis is usually encountered only after fourteen days or more of treatment, the possibility of the occurrence of this complication will be small if treatment is not continued more than twelve days. No serious toxic effects have been reported in any of the cases of undulant fever treated with sulfanilamide to date.

#### COMMENT

Many forms of treatment are employed in undulant fever. Among these are immune serum therapy, vaccines, hyperpyrexia induced by mixed typhoid vaccine or artificially, as well as the administration of foudrin, neoarsphenamine and other similar drugs. None of these methods has been proven to be uniformly successful in different clinics. Some of these therapeutic agents are not readily available, and some result in serious systemic reactions.

The success with which undulant fever has been treated with sulfanilamide and related compounds in clinics scattered throughout America and Europe is most encouraging. The fever and symptoms have usually disappeared after two to twelve days of treatment with sulfanilamide. Most of the reported cases have been treated with this drug within the first two months after the onset of symptoms. There is as yet no satisfactory body of evidence regarding the effectiveness of the drug in cases of longer duration.

Although single relapses have occurred in approximately 20 per cent of the cases which responded to sulfanilamide treatment, it appears that the dosage in many of these cases was too low and that relapses may not occur in any of the adequately treated cases. When relapses have occurred, the fever and symptoms have been controlled with a second short course of sulfanilamide therapy.

The drug is easily available and the toxic manifestations are usually mild. Because of occasional serious toxic effects which may occur in any diseases in which this drug is admin-



istered, daily visits by the physician and daily studies of the hemoglobin of the blood and of the white blood cell count are strongly advised during administration of the drug

The findings, following sulfanilamide treatment, of diminished agglutination titers and of negative blood cultures in cases which had shown positive cultures before treatment, bear further evidence that the infection is controlled

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### THE USE OF SERUM, SULFANILAMIDE, AND SULFAPYRIDINE IN THE TREATMENT OF PNEUMOCOCCIC INFECTIONS

#### TREATMENT OF PNEUMONIA

THERE are now three important agents that must be kept in mind in the treatment of pneumonia and other pneumococcic infections. These are specific antipneumococcic serums, sulfanilamide, and sulfapyridine. It is important for the physician to become acquainted with the field of usefulness of each of these agents and with their limitations.

**Serum Therapy**—Specific antipneumococcic serums have now been adequately proved to be effective agents in reducing the death rate and bringing about rapid clinical cures in cases of pneumonia due to pneumococci of many types, particularly Types I, II, V, VII, and VIII in adults, and also Type XIV in infants and children. The important features of successful serum therapy may be summarized briefly.

1 *Serum therapy is type-specific*. It requires careful bacteriological control. Present methods for typing are simple and rapid. The Neufeld method used directly on sputum gives results within a few minutes. In patients with few organisms, the same method applied to the peritoneal exudate of mice inoculated with sputum gives the results within three to five hours. The method is also applicable to materials obtained by pharyngeal culture in suitable media containing rabbit or horse blood, either directly or after mouse inoculation.

2 *Serums must be given intravenously*, proper precautions must be taken as in all serotherapy. These precautions

include a history of allergic manifestations and previous serum injection, as well as skin and ophthalmic tests and the so-called intravenous test. With these tests as a guide it is possible to avoid most of the important reactions or to control them as soon as they occur. The recent rabbit serums have reduced the incidence of reactions due to specific sensitivity and have thus eliminated many of the early allergic reactions.

3 *Serum is most effective when used early in the disease* This is probably due to the fact that the body defense mechanisms, namely, the leukocytes and perhaps the fixed phagocytes, play an important part in ridding the body of the infecting organism. The process is made possible by the injected antibody.

4 *The dose of specific serum must be adequate*, the proper dose varies with the individual case. In general, the smaller doses are successful in young individuals with sterile blood cultures early in the disease before the process has extended beyond a single lobe and when complications are not present. In most instances uncomplicated pneumonia in a person under twenty-five or thirty years of age of four days' duration or less yields with rapid crisis to the introduction of 40,000 to 80,000 units of serum. In infants and children, doses of 10,000 to 30,000 units are often adequate. These doses are probably sufficient for most types other than perhaps Type II. The doses are increased with age, with delay in treatment, or when the pulmonary process is extensive, and are doubled in patients with bacteremia, in those who are pregnant, or in whom there is reason to believe that purulent complications have begun while the pulmonary lesion is still active.

Failures of specific serotherapy can usually be explained by one or more of the following:

1 *Inadequate dosage* This includes dosage which, in amount, appears to be adequate but which is given over too long a period of time. A dose of 100,000 units given within a period of two to four hours in an ordinary case is considerably more effective than the same dose given as 20,000 units every six or eight hours. In severe cases, especially, is this important, since a dose of 200,000 units in a bacteremic patient may bring about an immediate recovery whereas 400,000 or even 500,000 units spread over a period of two to five days may have no effect.

2 *Delayed treatment* With the serums now available, given in proper doses, good results may be obtained through the fifth day of the illness except in some fulminating cases or in some older patients, or in patients with other complications. However, late cases may be benefited.

3 *Mixed infections* The hemolytic streptococcus is an organism which frequently gives rise to infection, either along with or following recovery from pneumococcal infection. More than one type of pneumococcus is sometimes involved in certain cases. With pneumococci of the higher types, it is sometimes difficult to determine which of multiple organisms is important unless the blood stream is invaded or the organism is obtained directly from the lung or from an infected exudate. The predominant organism in a good specimen of sputum raised from the bronchi can usually be considered as important. The relative number of pneumococci of different types that may be present in the same sputum can now be determined directly by the Neufeld method.

4 *Errors in typing* These are now relatively infrequent with experienced technicians.

5 *The presence of complications* Either purulent complications of the pneumonia or systemic complications not related to the pneumonia may interfere with successful serum therapy.

The greatest recent advance in specific serum therapy has been the introduction of rabbit serums. These serums have provided antibodies in considerably greater concentration which are apparently much more effective, except perhaps in Types I, V, and VII. Moreover, such rabbit serums are available for practically all the pneumococcus types. With these serums, immediate "allergic" reactions are rare. Thermal reactions (chills) with the recent serums have become considerably less frequent and are usually mild. Serum sickness is not a very important factor. While the milder manifestations occur in 20 per cent or more of serum recipients, severe discomfort is rare.

These serums are now applicable to the treatment of about two-thirds of all the cases of pneumococcal pneumonia. In such cases the death rate can be reduced to less than one-half for all cases and to less than one-third in those cases treated on or before the fifth day. Serum treatment alone has not

been highly successful in the treatment of cases of Type III pneumococcic pneumonia, although striking responses have been observed in many cases, particularly early cases before the blood stream has become invaded

**Sulfanilamide.**—There is a definite rationale for the use of sulfanilamide in the treatment of pneumococcic infections. This agent, in concentrations attainable in human therapy, is definitely bacteriostatic for many types of pneumococci. In certain experimental pneumococcal infections it has shown definite therapeutic value. Used in conjunction with specific serums, sulfanilamide has enhanced the therapeutic efficacy of serum and is considerably more effective than either the serum or the drug used alone. A number of reports of results from the use of sulfanilamide alone in the treatment of pneumococcal pneumonias have indicated that the drug may have some effect. This has been noticeable particularly in the treatment of cases of pneumococcus Type III pneumonia. In our own experience it has been difficult to ascribe to this drug alone any great curative effects in many typical cases of pneumococcal pneumonia. Dramatic responses to its use, such as we have been accustomed to see with specific serum or, more recently, in cases treated with sulfapyridine, are rare. The results, in general, are those which could be expected with an agent which is strictly bacteriostatic, that is, the patient in whom the drug is effective remains febrile and the disease remains more or less stationary until about the time of the expected crisis. Some cases with low-grade infection or those treated late are apparently benefited most, presumably for this reason. Other cases with low-grade bacteremia have shown clearing of the blood stream in some instances, but in many cases the bacteremia was not affected.

Sulfanilamide is most useful as an adjunct to specific anti-pneumococcic serums.

**Dosage**—It is probably necessary, in order to get any therapeutic effect from sulfanilamide in pneumococcal pneumonia, to maintain in the blood a concentration of between 7 and 10 mg per 100 c c of the free or non-acetylated form of sulfanilamide. To maintain this level in the average adult it is usually necessary to give an initial dose of 4 to 6 gm (60–90 grains) within a period of two to four hours, and then to maintain a dosage of 1 gm (15 grains) every four hours.

Because this drug is excreted with fixed base and tends to produce acidosis, it is necessary to give alkali in the form of bicarbonate of soda, about 10 grains with each dose. In patients in whom the renal function is impaired, excretion of the drug may be slower and higher levels may be attained with smaller dosage. In many cases of pneumonia, however, it is difficult to maintain the desired concentration even with the dosage mentioned, presumably due to irregularities in absorption. The dosage must necessarily be adjusted by determining the concentration in the blood. The fluid intake may be safely curtailed in most patients to between 2,000 and 2,500 c.c. a day provided there is no excessive sweating. The toxic effects of sulfanilamide observed in cases of pneumonia are similar to those observed with its use in other infections.

**Sulfapyridine**—There can be little doubt now that the introduction of sulfapyridine into the therapy of pneumonia has been the greatest advance made in the treatment of this disease. In contrast to sulfanilamide, there is evidence that this drug may exert a bactericidal as well as a bacteriostatic action on pneumococci of most of the types. Furthermore, and presumably because of this bactericidal action, it may be active without the aid of body defenses. Like sulfanilamide, however, it is considerably more effective when used in combination with specific serum than when either the serum or the drug is used alone, and the effect is then exerted with lower concentrations of the drug and with smaller amounts of antibody. In the case of specific serum, an intact body mechanism is necessary for its action and, partly for this reason, serum may not be effective when used late in the disease. Sulfapyridine, on the other hand, may be effective at any stage.

Sulfapyridine has already been demonstrated to be an important life-saving measure and has reduced the mortality from pneumonia of all types beyond any question of statistical significance. By virtue of its more universal application, the reduction in death rate is considerably greater than that attainable with specific serums. It cannot be determined on the basis of the data thus far available whether the drug is more effective than good specific serums properly used in those cases where the latter have been demonstrated to be effective.

There is already evidence that the drug is useful in pneumonias due to many if not all of the types of pneumococci.



It is effective in cases in which multiple pneumococcus types are encountered in the sputum, and in some instances in which pneumococci, together with other organisms, are found. It is probably also effective in hemolytic streptococcal infections, but there is no evidence that it is more effective than sulfanilamide. There are conflicting data concerning its efficacy in pneumonias due to *Staphylococcus aureus*, but the data thus far available would seem to indicate that the drug may have some beneficial effect, at least in certain cases of pneumonia due to this organism. There are also certain obvious advantages in the use of the drug in cases where serum therapy is used with hesitation. These are patients with "known allergy," patients with congestive cardiac failure or with cardiac arrhythmias, and very old patients. In these patients the risks of untoward reactions from serum are of great importance. To be sure, recent serums have been used successfully in such cases.

In addition to saving lives, the acute febrile and toxic course of the disease is definitely curtailed when sulfapyridine is used. In most instances, where the drug is properly tolerated and adequate dosage is used, the fever and elevated pulse rate subside within from eighteen to forty-eight hours of beginning treatment. However, this course of events in sulfapyridine treated cases is somewhat different from the same drop in fever and pulse rate observed following adequate specific serum therapy. Following adequate doses of specific serum, the patients are usually entirely free of all toxic symptoms and look and feel well. After treatment with sulfapyridine, patients may still exhibit evidence of activity of the pulmonary lesion and may feel ill and depressed from the toxic effects of the drug. In certain cases in which sulfapyridine has been continued for a period of forty-eight hours or even longer after the subsidence of fever, recurrences of the pneumonia have been noted after the drug is discontinued. These were evidenced by relapse of fever, elevated pulse rate, rusty sputum, and extension of the process in the lung. In such cases the same organism is usually recovered, but other types of pneumococci or other organisms are sometimes found.

Sulfapyridine therapy has certain unfavorable aspects. In the first place, its absorption, excretion, and degree of acetylation are very irregular in different patients, and these factors

cannot be predicted. There is reason to believe that the optimum dose is that which results in a concentration in the blood of 4 mg or more per 100 c.c. of the non-acetylated form of sulfapyridine. However, many cases have shown typical favorable responses on doses which are usually considered to be adequate but the concentration of the drug in the blood never reached levels above 1 or 2 mg per 100 c.c. In some patients with nausea and vomiting, adequate blood levels are not attained whereas, in others, the levels may be higher than in similar patients on the same dose who do not vomit.

*Toxic Reactions*—The common toxic effects of this drug are now fairly well recognized. Most common is nausea, which occurs in about two-thirds of the patients and is associated with vomiting in about a third of the patients. These symptoms are sometimes observed after the first dose, but they more often begin after several doses have been taken. Some patients vomit almost immediately after taking the drug. This symptom is sometimes lessened by administering the drug crushed in milk or in water, or mixed with some semi-solid food. The vomiting may be severe enough to cause marked dehydration and necessitate the administration of fluids parenterally. In some cases it is almost impossible to continue oral therapy without extreme discomfort. In other cases vomiting and even nausea subside while the drug is being taken regularly. Sedation may help in some cases.

Hemolytic anemias, both the severe acute type that develops on the second to fifth day and the milder, delayed type, may occur with this drug. These anemias are similar to those seen in patients treated with sulfanilamide but are probably less frequent. Leukopenias, however, are somewhat more common, they may occur early, and are often merely transient. Agranulocytosis has been observed, usually after ten days or more of treatment, although we have seen one case in which it developed in thirty-six hours. Marked mental and physical depression may occur after the fever and pulse rate have declined. These may be independent of nausea. Occasional patients exhibit moderate or pronounced excitement and delirium following the subsidence of fever.

Drug fever and morbilliform eruptions, and occasionally scarlatiniform eruptions, have been noted. These are no more frequent than with sulfanilamide. The diagnosis of drug fever

in patients with pneumonia treated with sulfapyridine is rather difficult since it occurs at about the time when complications or extension of the pulmonary process may occur. It also occurs when serum sickness would be expected if specific serum is used. With the appearance of rusty sputum or the physical signs of extension, or when there are signs of fluid in the chest or other evidences of focal complications associated with leukocytosis, the drug may be continued. In the absence of such symptoms it may be necessary to discontinue the drug in order to determine the possible relationship of the drug to the fever. The appearance of rash is usually an indication for discontinuing the drug. Fever with a rash not attributable to serum sickness or to other medication may be considered to be due to sulfapyridine, and the latter should be discontinued under such circumstances.

Cyanosis has been considerably less frequent with this drug than with sulfanilamide. Acidosis is not a feature of therapy with sulfapyridine and, therefore, alkalis are not an essential part of the treatment as they are with sulfanilamide. When hemolytic anemia of the acute variety occurs, particularly if associated with hemoglobinuria, alkalis should be given in amounts sufficient to result in the excretion of an alkaline urine.

One of the most important complications of sulfapyridine therapy concerns the renal function. Hematuria has been noted with considerable frequency and has often been associated with symptoms suggesting renal colic. Nitrogen retention and edema, with or without hematuria, have also been noted. Fatalities due to this complication have been observed. In most instances when this complication was recognized, if the drug was discontinued or its dosage reduced and an adequate supply of fluid administered, these toxic effects subsided. This complication is probably due to the fact that the drug is concentrated in the urine and is excreted largely in the acetylated form. The acetyl-sulfapyridine is considerably less soluble than the non-acetylated form, and the concentration of this material in the urine, and perhaps in the kidney, may be such as to result in the precipitation of crystals. Such crystals have been seen in the kidney pyramids, and concretions of the crystals in stones of various sizes have been noted in experimental animals and in fatal human cases in the pelvis of the kidneys,

in the ureters, and in the bladder. Frequently crystals are seen in the voided urine.

It is obvious that in patients who are under treatment with this drug, careful observations must be made of the blood and urine for the development of anemia, leukopenia, hematuria, and nitrogen retention. The fluid intake must be maintained, by parenteral routes if necessary, in order to avoid hemoconcentration, and also to avoid the possible renal irritation from the concentrated drug.

*Dosage*—The exact dosage of the drug is not known, nor is it definitely known how long treatment with this drug should be continued or, rather, how soon it may be safely discontinued. Good results have been obtained with widely varying doses. The dose most frequently used for the average adult is an initial dose of 2 gm followed by 1 gm every four hours until the subsidence of fever, and then 1 gm every six hours for from four to seven or eight days more. Relapses have been observed when the drug has been discontinued after periods of three or more days following the subsidence of fever. Our observations have indicated that in patients treated with sulfapyridine, specific immunity develops at the usual time, which is rarely before the fifth day and frequently is delayed until the tenth day or later.

It is felt by some observers that the treatment should be continued until the time when natural immunity has developed. Since this time varies so widely in different patients, no categorical statement can be made as to the optimum time for discontinuing treatment. It is to be recalled, however, that the longer treatment is continued, the more opportunities there are for serious toxic effects to occur. It is obvious that where immunity is given artificially by means of specific antipneumococcus serums, the danger of relapses, at least with the same organism, is practically eliminated. Treatment with the drug, therefore, can be more safely discontinued early if serum is also used.

**Combination of Serum and Sulfapyridine**—It is evident from what has been said that both serum and sulfapyridine are highly effective agents. The problem is to determine whether specific serums are necessary, or under what conditions specific serums exert additional benefit in reducing the death rate or in curtailing the discomforts of either the disease

or its treatment. Those clinicians without experience in serum therapy, particularly those who have not had an opportunity to use adequate amounts of good concentrated serums, especially the more recent rabbit serums which are relatively free of untoward reactions, do not consider that serum therapy has any further place in the treatment of pneumonia. On the other hand, those who have used these serums intelligently have been so thoroughly impressed with the results in individual cases and with the effects on the death rate that they have been loath to give up this very important therapeutic agent.

Furthermore, from theoretical as well as practical considerations it is obvious that the combination of serum and sulfapyridine is the method of choice, since treatment can be curtailed sooner and probably considerably smaller amounts of antibody are necessary to attain an adequate therapeutic response. Furthermore, it is important for physicians to be acquainted with both the beneficial and the untoward effects as well as the limitations of both types of treatment so that either or both can be used in any given case.

From this point of view, it is best in the treatment of pneumonia for the physician to be prepared to give serum in every case by obtaining sputum for typing and blood for culture *before treatment with sulfapyridine is begun*. If, then, the patient is made too uncomfortable from the toxic effects of the drug, or if the response to the drug is not adequate, he will immediately have available another therapeutic agent which may rapidly bring about the desired therapeutic response.

Because the specific serums are so highly effective when used early in the disease and since complete alleviation of symptoms may be brought about very rapidly by the use of such serums, this mode of treatment may still be preferable in cases due to the common types, other than Type III, when they are diagnosed before the end of the fourth day. The inconveniences of drug therapy for both patient and physician may thus be avoided. In certain other patients it is still advisable to give serum alone whenever feasible. These include patients with hepatic or renal disease, patients with granulocytopenias, those with severe nausea and vomiting, and particularly those in whom the pneumonia complicates abdominal operations.

It would seem desirable in certain cases where the expected

fatality from the disease is known to be high, such as in patients with bacteremia, in pregnant women in patients over forty years of age, and perhaps in late cases treated after the fourth day when patients are still very sick and toxic from the disease, to begin treatment with both serum and drug simultaneously. It may be possible in such cases to institute treatment with sulfapyridine as soon as the clinical diagnosis is made and then to begin serum therapy when the etiologic diagnosis is established. In type III pneumonia it is felt that sulfapyridine should always be given for about twelve hours before any serum treatment is started.

#### TREATMENT OF PNEUMOCOCCIC EMPYEMA

This complication is said by some workers to be more frequent following chemotherapy than in untreated controls. In some reports concerning serum therapy, empyema has been as frequent and sometimes slightly more frequent than in non-serum treated cases. This apparent paradox is not too difficult to explain. Any life-saving measure in the treatment of pneumonia will keep alive severely ill patients with positive blood cultures. In this group of patients, empyema is most frequent. While empyema may be aborted in the milder cases treated early, it is not often affected in those cases in which the complication has already become established at the time treatment is begun, whether with serum or drug. In some cases in which thin, purulent exudates containing pneumococci are obtained during the acute disease or soon after the fever subsides, the fluid may resorb completely without resort to surgical measures. This is true both in patients treated with specific serums and among those treated with sulfapyridine. It is occasionally true when neither agent is used.

Treatment with serum and sulfapyridine is recommended in cases in which thin, purulent fluid is obtained during the active pneumonia or sulfapyridine alone when the pneumonia is apparently subsiding. While sulfapyridine, like sulfanilamide, is well distributed in all body fluids and can be recovered in only slightly lower concentrations in pleural fluid than in the blood, sterilization of such infected pleural exudates has not been frequent and the disease most often takes its usual course.

Open thoracotomy must be resorted to in most instances

## TREATMENT OF PNEUMOCOCCIC MENINGITIS

It is fair to say that, before the advent of sulfanilamide, the percentage of cases of recovery from pneumococcic meningitis was extremely small. Occasional recoveries had been noted, but no type of treatment was associated with frequent cures. Specific antipneumococcic serums alone, given by all routes and combined with frequent or forced lumbar drainage, have been successful only in occasional cases, usually those in which a purulent focus was responsible and in which that focus was removed. Recoveries under these conditions have been reported even without specific serums and only with frequent or constant drainage of cerebrospinal fluid.

Following the introduction of sulfanilamide there appeared a number of reports of individual cases or groups of cases of pneumococcic meningitis in which recovery occurred following the use of this drug, either alone or in combination with specific serums. In a number of cases where we had an opportunity to make intensive studies it was felt that specific antipneumococcic serums should form an important part of the treatment. Furthermore, it was frequently necessary to introduce small amounts of antibody and complement (obtainable from fresh human serum) intrathecally. The optimum treatment that we recommended was as follows:

- 1 Preliminary lumbar puncture should be done for diagnosis and for the typing of the pneumococcus. Typing can frequently be carried out directly on the fluid by the Neufeld method.

- 2 If purulent fluid is obtained, a blood culture should be taken immediately. Cultures of blood or of spinal fluid taken after chemotherapy is instituted may show no growth or delayed growth due to the bacteriostatic action of the drugs.

- 3 Treatment with sulfanilamide is instituted forthwith. A large single dose of 4 to 8 gm. is given, either by mouth or in an 0.8 per cent solution in physiologic saline subcutaneously. This is followed by regular dosage of 1 gm. every four hours for the average adult, this being given by mouth or through a nasal tube together with a similar or slightly smaller amount of bicarbonate of soda. In infants and children the usual dosage required is somewhat higher than the amount calculated on the basis of the weight. The object of the dose chosen is

to maintain a level of about 10 mg of the free sulfanilamide per 100 c.c. of spinal fluid or blood. The concentration of the drug should be determined frequently and the dosage adjusted accordingly.

4 Lumbar punctures are repeated, at first three or four times a day, and then less frequently as the cerebrospinal fluid pressure reaches normal and the fluid becomes and remains sterile, and as its cytology and chemistry approach normal.

5 As soon as the type is determined, specific antipneumococcus serum is given intravenously. The dose of antibody usually necessary is between 100,000 and 300,000 units or more depending upon whether or not the blood culture is positive. The object of the intravenous serum is to establish an adequate balance of antibody in the circulating blood.

6 When such a balance of antibody is established, venous blood in amounts of 20 c.c. may be withdrawn from the patient, the fresh clear serum rapidly separated, and then injected intrathecally at the end of the next lumbar drainage. This latter procedure may be repeated until the cerebrospinal fluid becomes normal. In infants or children, 5 to 10 c.c. of fresh, normal human serum and 0.5 to 1.0 c.c. of therapeutic serum may be used instead of the patient's own serum.

7 Foci of infection, such as mastoiditis, sinusitis, and infected fracture wounds, must be eradicated, surgically if possible. These operations may be undertaken as soon as the patient has received an adequate amount of sulfanilamide and, preferably, after serum therapy has already been instituted.

8 Transfusions of citrated blood are given when the hemoglobin falls below 60 or 70 per cent.

Failures from this form of therapy are still frequent, particularly in patients in whom the local purulent foci were not eradicated and in patients who had already developed endocarditis. One unfortunate aspect of this treatment, when it is not rapidly and completely successful, is that the patients may look and feel improved and the spinal fluid may clear partly but never become quite sterile. In such cases death may be delayed as long as five or six weeks.

More recently, reports have appeared of recoveries from pneumococcal meningitis with the use of sulfapyridine, either alone or in combination with specific serums. With this drug the levels attainable in the spinal fluid are about two-thirds



those in the blood. Because of the experimental evidence for the superiority of this drug over sulfanilamide in pneumococcic infections, sulfapyridine is theoretically preferable. Our own experience to date has not demonstrated this superiority in this condition. In fact, as compared with sulfanilamide, we have found it considerably more difficult to sterilize the cerebrospinal fluid after the use of sulfapyridine in massive doses when high concentrations were attained in the blood and spinal fluid. The significance of this difference is not yet clear.

#### TREATMENT OF PNEUMOCOCCIC PERITONITIS

A number of favorable results have been noted in the treatment of primary pneumococcic peritonitis with specific anti-pneumococcic serums. The greatest benefit is obtained if the treatment is undertaken early in patients with positive blood cultures. Operations have been avoided in such cases. Where operations had already been done, the institution of specific serum therapy has brought about more rapid recoveries. Sulfanilamide alone has also proved successful in some such cases. The combination of sulfanilamide and specific serums is obviously the better mode of attack. Both drug and serum are given in full doses as in cases of meningitis, the serum being given intravenously. The drug may be given subcutaneously at first and then continued orally, or, repeated subcutaneous injections may be necessary.

In this condition also, recoveries have been reported recently with the use of sulfapyridine alone or with specific serums. The question of operative interference has not been settled. Sulfapyridine and serum may be used both as a preparation before operation, or later in those cases in which the diagnosis is made during or following operation.

#### TREATMENT OF OTHER PNEUMOCOCCIC INFECTIONS

**Otitis Media and Mastoiditis** — There is some evidence to indicate that sulfanilamide and sulfapyridine may have some effect on preventing the occurrence of mastoiditis following acute purulent otitis media. In a number of cases the discharge and the acute symptoms of mastoiditis clear rapidly. However, the infection may lurk and operation may become necessary at a future time. Exact data indicating to what

extent operations may be averted are not yet available. The chronic cases are probably not affected.

In general, when there are focal infections which can be drained, open surgical drainage and removal of necrotic bone is the only curative treatment. Sulfanilamide or sulfapyridine may be useful in such cases to prevent extensions or metastatic infections.

**Pneumococcic Endocarditis**—There is no evidence that any form of treatment, either specific serum, sulfanilamide, or sulfapyridine, has any effect on this condition when it has become established.

Specific serum in particular has no effect since in most instances endocarditis is a late complication of pneumococcic infections and is frequently associated with circulating type-specific antibodies for the pneumococcus involved. Treatment with bacteriostatic drugs like sulfanilamide or sulfapyridine often makes it difficult to culture pneumococci from the blood, at least temporarily. Some patients with endocarditis who tolerate the drug well may feel considerably improved while under treatment with sulfapyridine, although the blood continues to be invaded.

#### SUMMARY AND CONCLUSIONS

Both specific antipneumococcic serums and sulfapyridine are highly effective agents in the treatment of pneumococcic infections. Either agent alone may be effective in most cases of pneumonia due to specific pneumococcus types. Treatment with the combination of specific serum and sulfapyridine is highly effective in the cases with the worst prognosis. Both serum and sulfapyridine should be used in the treatment of meningitis or peritonitis due to the pneumococcus.

The present conclusions must be considered tentative, however, until more data become available with regard to the beneficial results and the side effects of sulfapyridine and the newer antipneumococcus rabbit serums, and until more information is acquired concerning the proper use of these two agents separately or in combination.



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### THE USE OF SULFANILAMIDE IN INFECTIONS OF THE URINARY TRACT

ACUTE and chronic infections of the urinary tract are conditions commonly encountered in the practice of medicine and they not only cause periods of acute disability, but lead to serious late effects in the form of hypertension and renal failure<sup>1 2</sup>. Careful study and management are therefore desirable in every case in order that immediate and permanent cure may be effected.

Clinically, there may be the signs of renal infection alone, with chills, fever, and pain in the flanks and back, or there may be infection of the bladder, with pain above the pubis, dysuria, hematuria, and frequency. Certain cases will present features suggesting that both the upper and lower urinary tracts are involved, in almost every case white blood cells and bacteria will be found in large numbers in the freshly voided specimen. It is of great importance that the latter be studied by means of smear and culture in order that the etiologic organism may be identified.

The pathologic physiology, bacteriology, and anatomy of this group of diseases is of interest. Interference with the free flow of urine from the kidney or bladder has long been known to predispose these organs to infection, and this will be found in many cases. Urethral stricture and hypertrophy of the prostate in the male, the gravid uterus and cystocele in the female, renal calculus, torsion or constriction of the ureter, primary or metastatic malignant disease, and disturbance of the innervation of the bladder in both sexes are the commonest causes of disturbances of urinary drainage.

In the vast majority of cases of infection involving the kidney alone, *Bacillus coli* will be found to be the etiologic bacterial agent, especially if obstruction is present. *Staphylococcus aureus*, the influenza bacillus, and various members of the enteric group are less frequently found. Other organisms may be isolated in infections involving the bladder, especially *Streptococcus faecalis*, *Staphylococcus albus*, and *Bacillus proteus*. The last organism is most often associated with marked obstruction or deformity of the urinary passages. Mixed infections occur most frequently under similar circumstances, although they are common in their absence.

Diffuse inflammation of the involved portion of the urinary tract is present in many cases of infection of these organs, with hyperemia, necrosis, and sloughing of the mucosa. Cellular infiltration, organisms, and small abscesses will also be found in most instances in the deeper tissues, particularly among the tubules of the kidney.<sup>2</sup> This is important in the consideration of therapy as bactericidal substances excreted in the urine will not come in contact with these deep areas of inflammation.

Healing occurs by means of the usual mechanism through which the body disposes of bacterial invaders with the formation of scars.

Treatment of this group of infections has consisted in the removal of the obstruction to the free flow of urine and the administration of substances which, when excreted in the urine, might be bacteriostatic or bactericidal. The former may be partially accomplished by increasing the urinary output, while various surgical procedures may lead to permanent relief.

Drug therapy has, until recently, been unsatisfactory. Methylene blue, acriflavine, pyridium, and hexamethylenamine have been widely used, with indifferent results. The introduction of the ketogenic diet by Clark<sup>3</sup> and of mandelic acid by Rosenheim,<sup>4</sup> with the demonstration that by these means a bactericidal urine was excreted, gave new impetus to the careful treatment of urinary infections. Since acidification and concentration of the urine are necessary, and since nausea, vomiting, and anorexia often follow their use, these methods have not been applicable to every case.

The report that sulfanilamide was effective in certain of these infections was therefore received with great interest, for

here was a remedy of theoretical value. Excreted by the kidneys in high concentration, bacteriostatic and bactericidal for many organisms, diffusing freely through all the body tissues, permitting attack on the deep-seated organisms, active regardless of pH, easily administered and relatively free of serious toxic action, sulfanilamide seemed an agent of great promise. It has therefore received wide clinical trial in the treatment of infections of the urinary tract.

Laboratory studies have demonstrated certain features in regard to the mode of action of sulfanilamide against the organisms commonly found in the urine. Kenney<sup>5</sup> and Helmholtz<sup>6</sup> described experiments in which the bacteriostatic and bactericidal effects of sulfanilamide were demonstrated toward *B. coli*, *B. proteus*, and staphylococci, but not *Streptococcus faecalis*. They used concentrations of the drug of from 50 to 100 mg per 100 c.c. of urine, and the latter author suggested that it was more effective in an alkaline urine. More recently, Long and Bliss,<sup>7</sup> and Vest, Hill and Colston,<sup>8</sup> have confirmed the bacteriostatic and bactericidal effect of the drug for the organisms usually involved in infections of the urinary passages, but have added evidence that it may be necessary to increase the urinary concentration of the drug to 750 mg per 100 c.c. in order to obtain a striking effect in the presence of large numbers of organisms and resistant strains.

In this clinic it has been possible to produce bacteriostasis, and in certain instances the killing of large numbers of organisms, but no important increase in the activity of the drug has been observed with more than 150 mg of the free drug per 100 c.c. of urine. The hydrogen ion concentration apparently had no demonstrable effect within the physiologic range of pH 5.0 to 8.0.

It is possible to obtain these levels of sulfanilamide in the urine with a dose of from 3 to 4 gm (45 to 60 grams) a day if the urinary excretion is approximately 2000 c.c. Clinically, a much smaller dosage and concentration in the blood and urine may be entirely adequate, and no correlation has been possible between the *in vitro* studies and results in the individual patient.

The clinical aspects of the use of sulfanilamide in instances of infection of the urinary tract may best be considered by dividing these cases into broad groups.

## ACUTE PYELONEPHRITIS

Many features of the use of sulfanilamide in acute infections of the kidney can be illustrated by the presentation of a case

**Case I**—A young primipara in the second trimester of an otherwise normal pregnancy was admitted to the hospital with chills, fever, and pain in the left flank accompanied by pyuria and *B coli* bacilluria. So severe and prostrating was the illness that the diagnosis of perinephric abscess was repeatedly entertained. The usual conservative measures, continued for five weeks, failed completely to effect any appreciable relief, and bouts of fever continued to occur. This patient's hospital course is shown in Fig 77. In the fifth week, during a marked febrile reaction, sulfanilamide was given by

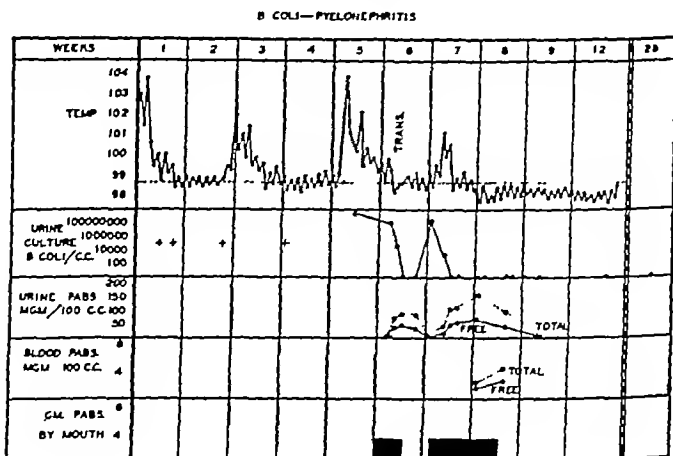


Fig 77—Hospital course in Case I

mouth in a dose of 4 gm (60 grains) a day in divided doses. The urine was sterilized promptly and the patient improved, administration of the drug was then discontinued, with the result that fever recurred and bacteria reappeared in the urine. Readministration of the drug promptly caused remission of all signs and symptoms. Continuation for seven days after the first sterile urine culture accomplished permanent cure. This patient was later delivered uneventfully of a normal child and, when last seen one year later, had remained well. At this time the urine and renal function were normal.

The features of interest in this case are the presence of pregnancy, the unremitting severity of the infection before treatment was begun, the inapplicability of any other remedy, the dramatic response to the first course of sulfanilamide, the

relapse following its withdrawal, and the prompt and gratifying results associated with its readministration. Fluids were never restricted, anemia present at the onset was not aggravated, and it should be especially noted that the concentration of the uncombined drug in the blood and urine was never more than 4.0 and 75.0 mg per 100 c.c., respectively.

These results are to be expected in approximately 80 to 90 per cent of all cases of acute pyelonephritis due to *B. coli* treated by sulfanilamide<sup>5, 9, 10</sup>. If there is no past history of infection of the kidney or demonstrable obstruction to the free flow of urine, or if the latter is present and may be eliminated, then a permanent cure may be expected.

A dose of 3 to 5 gm. of sulfanilamide per day by mouth, without limitation of fluid intake, is optimal and should be continued for from five to seven days after the first sterile urine is obtained or after the temperature has returned to normal. In those few instances in which bacteria persist, mandelic acid may be tried, however, this is to be avoided until some time after the acute phase of the disease since concentration of urine by limitation of fluids during this period is most dangerous.

Sulfanilamide is probably of no value in the acute coccal infections of the kidney occurring in the absence of obstruction.

#### CHRONIC PYELONEPHRITIS

The value of sulfanilamide is less clear in those instances of infection of the kidney in which chronic inflammation persists, with the development of contracted kidney, renal failure, and hypertension, in the absence of definite evidence of obstruction to the urinary flow. The course of events in such an instance are presented in Case II.

Case II.—A young woman was admitted to the hospital suffering from chills, fever, and pain in the right flank which had subsided rapidly on conservative treatment. She had had many previous similar episodes, and right nephropexy had been performed a few months before in the hope of securing permanent relief. There was no hypertension or evidence of renal failure, but pyuria and *Bacillus coli* bacilluria were marked. Retrograde pyelograms were approximately normal. For a period of more than six months she had been chronically ill and unable to work. Her course in the hospital is shown in Fig. 78.

Since the patient remained ill and bacteria persisted in the urine, sulfanilamide was administered in a dose of 3 gm. a day for eight days, with sterilization of the urine. Upon recurrence of bacilluria, the drug was again



administered in the same dosage for twenty-one days. On this regimen she improved very rapidly, with a return of the urine to normal and a gain in weight, strength, and sense of well-being. Two weeks after the course of sulfanilamide, organisms again appeared in the urine and there was a brief febrile episode. Mandelate therapy was then instituted under controlled conditions, but this failed materially to affect the urinary findings and was accompanied by nausea, anorexia, and loss of weight.

Two weeks later another period of acute illness occurred. This was treated with sulfanilamide in doses of 8 gm a day, which were continued for fourteen days, with the result that the urinary concentration reached a level of more

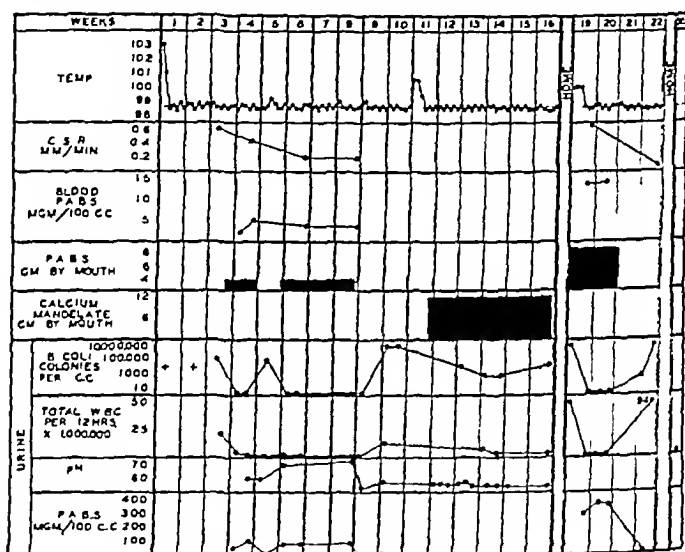


Fig 78—Hospital course in Case II

than 350 mg per 100 cc and that of the blood of 15 mg per 100 cc. There was no reaction to the medication and all signs and symptoms disappeared immediately. Ten days after this course the patient's urine was infected and she has since had several attacks of acute illness.

This case illustrates strikingly the tendency of certain cases of infection of the urinary tract to become chronic even in the absence of demonstrable urinary obstruction or deformity of the urinary passages. The interesting features of this case are the extreme chronicity of the pyelonephritis in which the urine could be sterilized readily with small doses of sulfanilamide by mouth but in which relapse nevertheless occurred regularly. Very large doses of sulfanilamide and a course of mandelic acid

were no more effective in promoting a permanent result. No toxic effects other than malaise and slight anemia with the second course accompanied the administration of the sulfanilamide, but the administration of the mandelic acid was associated with nausea and anorexia so severe that it could be continued only because of the great fortitude of the patient.

Cases of this type are common in medical practice, and the most exhaustive genito-urinary study frequently fails to discover abnormalities of the urinary tract susceptible of surgical intervention.

It is probable that the urine can be sterilized and the general health of the patient improved in many instances by the use of sulfanilamide in doses of 2 to 4 gm a day, although Long has described resistant cases in which much larger doses must be used. The treatment should be continued for from seven to ten days after the urine has become sterile and, if bacilluria reappears, it is useful to administer several courses of the drug, allowing a reasonable period to elapse between each course. If these dosage levels fail to effect a permanent clearing of the bacilluria, mandelic acid should be tried in the usual way before larger amounts of sulfanilamide are given.

More than 3 gm (45 grains) of sulfanilamide a day should not be prescribed for the ambulatory patient. It is essential that frequent visits to the physician, with complete examination of the blood, be made if sulfanilamide is to be used in any case.

#### CHRONIC INFECTIONS OF THE URINARY TRACT ASSOCIATED WITH MARKED STRUCTURAL ABNORMALITIES

In the large group of cases in which infection of the urinary tract is associated with serious structural disease of these organs, such as hypertrophy of the prostate, calculi, neurologic disease disturbing the innervation of the bladder, and malignant disease, sulfanilamide has proved to be more useful than any previous agent in the control of the symptoms and in effecting sterilization of the urine.

In general, bacteria can be eradicated from the urine in about 50 per cent of these cases<sup>8, 11</sup>, the extent of the underlying disease and the infecting organisms both affect the prognosis. Mixed infections are more difficult to treat than those due to a single organism, one variety frequently disappearing

only to leave the other in large numbers. *B. proteus* is to be found as an infectious agent almost exclusively in this group, and frequently it can be eliminated with great ease, an enormous advance over any other therapy previously directed against this organism.

Individuals suffering from cystitis with prostatic hypertrophy usually benefit greatly from the administration of small doses of sulfanilamide and the urine often becomes sterile. However, there is little evidence<sup>12</sup> that its routine postoperative administration after prostatectomy will markedly reduce the incidence of bladder infections during this period.

In general, the cases included in this group, and also the instances of cystitis associated with diabetes and various debilitating diseases, can usually be controlled by the administration by mouth of 1 gm. of sulfanilamide every twenty-four hours for each 1000 c.c. of urine voided during that same period. This dose may be safely continued for long periods of time and usually is not associated with toxic symptoms. Permanent cure is not to be expected unless the underlying structural changes can be eliminated.

#### TOXIC MANIFESTATIONS

The use of sulfanilamide in the treatment of infections of the urinary tract will be accompanied by all the usual and frequently described toxic side actions. Cyanosis, headache, nausea, anorexia, and malaise will frequently be observed and do not contraindicate the continuation of therapy unless they are severe. The development of marked anemia, dermatitis, fever, and agranulocytosis demand the immediate cessation of the drug and the administration of large volumes of fluid. Cases with marked renal damage should be carefully observed and the concentration of the drug in the blood determined by chemical means, in order that too large amounts may not be permitted to accumulate in the body.

#### SUMMARY

- 1 Sulfanilamide is a useful addition to the armamentarium of drugs used in the treatment of infections of the urinary tract.

- 2 It is easily administered and serious toxic reactions are uncommon.

3 It is effective against almost all of the ordinary organisms isolated from the urine, especially *Bacillus coli* and *Staphylococcus albus*

4 It frequently eradicates *Bacillus proteus*, an organism hitherto very difficult to attack successfully

5 Doses of 2 to 4 gm. a day by mouth are usually adequate, and the urine need be neither concentrated nor acidified

6 Sulfanilamide is most successful in treating acute infections of the kidney without permanent obstruction or a past history of infection

7 The urine may be sterilized in many chronic infections, but there is great tendency toward relapse

8 If marked structural abnormalities of the urinary tract are present, the urine can be sterilized in many instances and symptomatic relief obtained in others, but no permanent cure is to be expected unless the underlying disease state can be corrected

9 Sulfanilamide exerts the same toxic actions in these cases as in other conditions in which it has been administered

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## CLINIC OF DR CAROLINE A CHANDLER

FROM THE DEPARTMENT OF OBSTETRICS AND THE DEPARTMENT OF BACTERIOLOGY AND IMMUNOLOGY OF THE HARVARD UNIVERSITY MEDICAL SCHOOL, AND THE BOSTON LYING-IN HOSPITAL

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### SULFANILAMIDE IN THE TREATMENT OF POST-ABORTIVE AND PUERPERAL STREPTOCOCCAL INFECTIONS

PUERPERAL fever was clearly recognized as a disease entity by Hippocrates, Galen and Avicenna. Very little, however, was known of its origin or nature until late in the eighteenth century, when two English physicians, White<sup>1</sup> and Gordon,<sup>2</sup> published reports suggesting that the disease was contagious. In 1843, Oliver Wendell Holmes<sup>3</sup> read a paper before the Boston Society for Medical Improvement entitled, "The Contagiousness of Puerperal Fever," in which he pointed out clearly, for the first time, the transmissible nature of the disease. Four years later, in Vienna, Semmelweis<sup>4</sup> proved that puerperal fever was transmissible and therefore largely preventable. By the introduction of a single procedure, *i e*, disinfection of the hands of all persons attending obstetrical patients, the mortality rate from this disease was reduced by 75 per cent within one year. Finally, in 1879, Pasteur<sup>5</sup> first cultured streptococci from cases of puerperal infection. Although subsequent investigations have shown that other micro-organisms, such as the gonococcus, the staphylococcus, the pneumococcus, and the colon bacillus, are responsible for a certain number of puerperal infections, the vast majority of severe infections have been found to be caused by the hemolytic streptococcus.

#### THE HEMOLYTIC STREPTOCOCCI

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ferent strains, in which he distinguished between those which produced no hemolysis in blood agar plates (gamma) and those which produced either partial (alpha) or complete (beta) hemolysis in the same medium. The organisms commonly known as hemolytic streptococci all belong in the beta category. On the basis of a group antigen, designated the "C" substance, Lancefield<sup>7</sup> has divided the beta hemolytic streptococci into nine different serological groups—A, B, C, D, E, F, G, H and K. All human, pathogenic strains with rare exceptions fall into group A, strains producing mastitis in cattle into group B, strains from milk and cheese into still other groups, etc. Griffith,<sup>8</sup> by the technic of slide agglutination, has further subdivided group A strains into some twenty-five distinct serological types. A few types belonging to group A are pathogenic for man, and any type or strain can cause a variety of streptococcal diseases.<sup>9</sup> Commercial grouping and typing sera are available for diagnostic purposes, but so far, owing to the difficulty of producing streptococcal *antibacterial* sera commercially, there are no such sera for clinical use on the market. When specific antibody is needed in the treatment of septic streptococcal infections, the only source available is the blood of an immune donor.<sup>10 11</sup>

The hemolytic streptococcus produces at least five filterable exotoxins: (1) hemolysin, (2) leukocidin, (3) erythrogenic toxin, (4) fibrinolysin, and (5) the "spreading factor" of Duran-Reynals.<sup>12</sup> For the clinician, the erythrogenic toxin, which is responsible for the rash in scarlet fever, is of the greatest importance because it is capable of stimulating the production of a potent antitoxin in the animal body. Although two toxins, A and B toxins, have been identified<sup>13, 14</sup> in erythrogenic toxin, it is neither type-specific nor disease-specific. There is no such thing as scarlatinal erythrogenic toxin as differentiated from the erythrogenic toxin of erysipelas. The strain, Dochez N Y 5, most widely used in the production of commercial streptococcal antitoxin, elaborates both A and B toxins and stimulates the production of A and B antitoxins. Streptococcal (scarlatinal) antitoxin is, therefore, of value in treating the *toxic* manifestations of any streptococcal infection, regardless of the disease entity.

**Hemolytic Streptococci in Puerperal Infections**—The incidence of beta hemolytic streptococci in the vagina of

women during normal pregnancy is approximately 4 per cent<sup>15</sup> In normal parturient women, the incidence of *virulent* hemolytic streptococci is even less, as shown by the work of Smith,<sup>16</sup> Paine,<sup>17</sup> Colebrook,<sup>18</sup> Hare and Colebrook,<sup>19</sup> and Lancefield and Hare<sup>20</sup> Lancefield and Hare, for example, isolated only thirteen strains of beta hemolytic streptococci out of a series of 855 women cultured before delivery Only two of these thirteen strains were group A strains, and only one of the two resulted in puerperal sepsis Thus the incidence of group A strains in the human vagina before delivery is approximately 0.25 per cent On the other hand, in patients with severe puerperal infections, almost 100 per cent of the strains isolated fall into group A<sup>20</sup>

These studies indicate that infection occurs immediately before or after childbirth and that such infection is of exogenous origin Since 8 to 10 per cent of normal, healthy people harbor group A streptococci in their noses or throats during the winter months, the chief source of infection in these cases is obvious Direct evidence of this was furnished by Colebrook<sup>21</sup> who, in an extensive survey, found that approximately 70 per cent of the strains isolated from patients with puerperal sepsis were the same type as the strains isolated from the nasopharynx of attendant contacts or of the patient herself This clear-cut demonstration of the exogenous origin of puerperal infection emphasizes the necessity for flawless, aseptic technic and adequate masking in the delivery room

#### SULFANILAMIDE

The curative effect of prontosil on hemolytic streptococcal infections in mice was first demonstrated by Domagk<sup>22</sup> in 1935 His results were immediately confirmed by Levaditi and Vaisman,<sup>23</sup> and a short time later the Trefouels, Nitti and Bovet<sup>24</sup> reported that the active principle in prontosil and other related compounds was para-aminobenzenesulphonamide, now commonly known as "sulfanilamide" With this drug they obtained, in mice and rabbits, results fully as good as those obtained with prontosil

The earliest clinical trial of sulfanilamide was made by Colebrook and Kenny<sup>25</sup> in 1936 In a series of thirty-eight cases of puerperal sepsis treated with prontosil, only three deaths occurred, giving a case fatality of 8 per cent as com-

pared with a previous case fatality of 22.8 per cent. All but two of the strains isolated from the patients in this series were group A strains. These same authors,<sup>26</sup> a short time later, reported an additional twenty-five cases of puerperal sepsis treated with either prontosil or sulfanilamide in which no deaths occurred. All the patients in this series were infected with group A streptococci, with one exception, and six of the twenty-five had bacteremia (23 per cent).

In 1937, Colebrook and Purdie<sup>27</sup> reviewed the results of the treatment of 106 cases of puerperal fever with sulfanilamide and showed a striking reduction in the case fatality, from 22.8 per cent for 495 cases in the preceding five years, to 8 per cent for the treated group. One hundred of these patients were infected with hemolytic streptococci, ninety-two of which were group A strains, three were infected with an aerobic streptococci, and three with staphylococci. Two of the three patients with staphylococcal infections recovered, whereas all three of the patients from whom anaerobic streptococci were isolated died. Among the fatal cases infected with hemolytic streptococci, a group B strain was isolated in one instance and group G strains in two instances. Twenty-two of the 100 patients with hemolytic streptococci had bacteremia. Of these, six died, giving a case fatality of 27.3 per cent as compared with that of 71 per cent in eighty-two untreated bacteremic cases which occurred during a three-year period prior to the advent of sulfanilamide.

Lane-Roberts,<sup>28</sup> in a recent official report, presented a statistical analysis of all the cases of puerperal streptococcal infections which have been admitted to Queen Charlotte's Hospital in London over a seven-year period. The incidence of streptococcal infection during that period has been 1 in 700 cases admitted to the hospital, as compared with 1 in 115 cases on "district." The average case fatality in 500 cases, which occurred before sulfanilamide therapy was employed, was 22.6 per cent. Since the advent of sulfanilamide, 300 cases treated with the drug showed an average mortality of 5.3 per cent, and in 1938, out of over one hundred treated cases, there were four deaths, representing a mortality of a little less than 4 per cent.

The work of Colebrook and his co-workers has been confirmed by other investigators<sup>29, 30, 31</sup> and, even if one allows for

a slightly diminished severity in streptococcal infections within recent years, there is little doubt that sulfanilamide is of definite therapeutic value in puerperal sepsis. In view of the report by Hoare<sup>32</sup> on the prophylactic effects of the drug, its use as a protective measure in cases in which the risk of infection is great (prolonged and difficult labor, operative interference, upper respiratory or other infection at the time of delivery, etc.) is indicated.

#### FACTORS INFLUENCING RECOVERY FROM HEMOLYTIC STREPTOCOCCAL INFECTIONS

In the production of disease by any micro-organism two factors are involved, namely, the virulence of the organism and the resistance of the host. The virulence of the hemolytic streptococcus is determined by its ability to invade the host and multiply in the tissues, and by its capacity to elaborate toxins within the body. Toxicity and invasiveness are separate attributes of this organism. While some strains are both highly toxic and invasive, many strains are predominantly one or the other. Depending upon which element, the toxic or the septic (invasive), predominates, the clinical picture is primarily one of a toxic or septic character.

The resistance of the host to invasion by the hemolytic streptococcus depends upon an ability to destroy the organism and to neutralize its toxins. The ultimate mechanism of destruction of gram-positive cocci is that of phagocytosis plus intracellular digestion. Phagocytosis of *virulent* streptococci by human leukocytes depends upon the sensitizing action of specific antibacterial antibody.<sup>33</sup> Streptococcal exotoxins are not influenced by antibacterial antibody and require antitoxin for their neutralization.

The mechanism of infection and recovery in streptococcal disease is determined by the factors mentioned above. In local infections with organisms of low virulence, for example, recovery takes place through fixation of the infection at the local site without the development of circulating antibodies. Localized puerperal or post-abortive infections, in which the infecting strains are relatively avirulent, tend to remain confined to the uterus by the process of inflammatory fixation. Organisms of such low invasive power do not produce an antibody re-

sponse in the body, nor is antibody necessary, in general, for recovery from such infections. Treatment of infected abortions caused by non-invasive streptococci should be the treatment of any local infection, *i e*, drainage and removal of the focus of infection plus general supportive measures. If the infecting strain in such a case should, however, be a group A organism, sulfanilamide should be given preoperatively as a safeguard against a sudden increase in its virulence.

In local plus invasive infections with highly virulent strains (with or without bacteremia), recovery occurs by local fixation plus the development of immune bodies. In invasive streptococcal infections during pregnancy or the puerperium, highly virulent organisms rapidly invade the tissues and ultimately enter the blood stream unless the infection is controlled before bacteremia occurs. Recovery in such cases occurs by the process of local fixation plus the development of immune bodies. In untreated cases, if the organism is highly virulent and the patient possesses no antibodies to it, invasion of the blood stream takes place very rapidly and death results. If, in untreated cases, the infecting strain is moderately virulent and the patient possesses some antibody to it, local fixation may hold the infection in check until sufficient antibody is developed to prevent bacteremia or to control it if it occurs.

Although the mode of action of sulfanilamide is still not known, its bacteriostatic effect (*in vitro* and *in vivo*) on all types of group A streptococci has been demonstrated by many investigators. Whatever the mode may be, it acts on the organism in such a way as to enable the defense mechanisms of the body to overcome the infection. The drug, moreover, seems most effective against highly virulent strains,<sup>25</sup> avirulent ones being, in many instances, relatively insusceptible to its action.\*

With the foregoing considerations in mind, it is now possible to outline a rational method of treatment of post-abortive and puerperal streptococcal infections.

#### TREATMENT

**Sulfanilamide**—If the patient shows signs and symptoms of infection and/or beta hemolytic streptococci are present in

\* The drug should, however, be tried in chronic infections in view of the excellent results obtained by Purdie and Fry.<sup>21</sup>

cervical or intrauterine\* cultures, sulfanilamide should be administered as follows. The initial dose should be 0.3 gm (5 grains) per 10 pounds of body weight. Following the initial dose, 0.6 gm should be given every four hours until a total of 6 to 8 gm (for an adult of average weight) have been given in the first twenty-four hours. Thereafter, a daily maintenance dose of 4 to 6 gm should be given.

The concentration of sulfanilamide in the blood should be determined<sup>36</sup> within twenty-four hours after therapy is started. Following this, the blood level should be checked at daily intervals until the concentration of the drug is maintained steadily at a level of 10 to 15 mg per 100 c.c. When more or less constant, the blood level probably need only be checked every two or three days.

Therapy should be continued until signs and symptoms of the infection have been absent for four or five days. Red and white blood counts, as well as hemoglobin determinations, should be done within the first twelve hours after treatment is begun and thereafter at daily intervals. If signs of an acute hemolytic anemia or a marked agranulocytosis should develop, the drug should be stopped at once. The milder toxic symptoms, such as cyanosis, fever, dizziness, nausea, etc., rarely require any lowering of the dosage of the drug. Whether or not sodium bicarbonate should be administered together with the drug is still a disputed question, but until definite evidence to the contrary is presented, 1 gm of bicarbonate should be given for every gram of sulfanilamide as a safeguard against acidosis.

With regard to the use of sulfapyridine, M & B 693 and other related compounds in puerperal infections, there is no evidence to indicate that they are more effective therapeutically than sulfanilamide. Since the toxic effects of these compounds

\* Lochial cultures are of no value in establishing a laboratory diagnosis, especially in cases where specific therapy is dependent on the nature of the infecting organism. For this reason, all cultures in cases of suspected puerperal or post-abortive infections should be taken directly from the uterus by means of the Little<sup>37</sup> tube. Direct smears are of little value except in making a presumptive diagnosis, and therapy, therefore, cannot be based on them. If streptococcal infection is suspected from clinical evidence, sulfanilamide should be started immediately. A blood culture should always be taken *before* sulfanilamide is given because, later, cultures may not show growth owing to the bacteriostatic effect of the drug.

are more marked, sulfanilamide is the agent of choice in these infections

**Immune Transfusion** <sup>10, 11</sup>—Although sulfanilamide is effective against all types of group A streptococci, not all strains are equally susceptible to the action of the drug. Some strains are completely resistant (anaerobic ones especially), while others seem to require specific antibacterial antibody in addition to the drug for their destruction <sup>27, 28, 30</sup>. For this reason, blood transfusion from an immune donor is a valuable adjunct to sulfanilamide under the following conditions

In non-bacteremic, group A infections, sulfanilamide alone should be effective, but if no clinical response to the drug is apparent after forty-eight to seventy-two hours of treatment, immune transfusion is indicated—even in the absence of a positive blood culture. In bacteremic, group A infections, the antibody content of the patient's blood against her own organism should be determined <sup>10, 11</sup>. If little or no antibody is present, 300 to 400 c c of immune blood should be given. The antibody content of the patient's blood should be determined twenty-four hours after transfusion. If the phagocytic index is not increased at that time, immune transfusion should be repeated at daily intervals until there is a significant antibody response.

With regard to the selection of donors, since small amounts of antibody seem to be highly effective in conjunction with large doses of sulfanilamide,<sup>40</sup> time can be saved by doing the following routinely. Type ten donors and out of these select the ones having the highest phagocytic indices relative to the patient's index. Thereafter, transfuse as often as necessary with blood from this group.

**Erythrogenic Antitoxin**—In the presence of marked symptoms of toxemia (cutaneous rash, sustained elevation of temperature, persistently rapid pulse), as in puerperal scarlatina, erythrogenic antitoxin should be given. The dosage will vary with the severity of the case, but in the average case 8,000 to 12,000 units should be given.

The use of antitoxin should, however, be limited to definitely toxemic cases, because there is no evidence to indicate that it has any effect on the organism itself. It cannot, therefore, be expected to be of value in the treatment of septic, invasive streptococcal infections. Any reduction in case fatality

in puerperal fever which Lash<sup>41</sup> obtained by the use of his "concentrated streptococcus (hemolytic) antitoxic serum" could probably be explained on the basis of the unusually high incidence of toxemia (72 per cent in the treated group, 54 per cent in the control group) in his series. There is certainly no clear-cut evidence presented which would indicate that the antitoxic serum influenced the septic features of the disease, although it is difficult to analyze the material presented because of the numerous discrepancies between the tables and the text. The variation in the severity of streptococcal infections from year to year, however, is such that an analysis of a small group of cases over a ten-year period can have no statistical significance.

**Illustrative Cases**—The following case reports will serve to illustrate some of the points just presented.

The first patient, a twenty-four-year-old para II, was admitted to the Boston Lying-in Hospital at term with a diagnosis of sinusitis. Three days post-partum she developed a septic metritis. Group A, mucoid, virulent hemolytic streptococci were isolated in pure culture from the vagina, nose and throat. Sulfanilamide therapy was begun (80 grains per day). Because the patient's initial response to sulfanilamide was unsatisfactory, and because her blood contained very little antibody to the infecting strain, immunotransfusion was advised. Four immunotransfusions were given, together with 80 grain daily doses of sulfanilamide. Five days after the onset of the infection, the temperature reached normal. From then on, the patient convalesced rapidly to complete recovery and was discharged from the hospital nineteen days post-partum.

The second patient, a thirty-seven-year-old primipara, was admitted to the Boston Lying-in Hospital at term with a diagnosis of healing pulmonary tuberculosis. Acid-fast infection had been first diagnosed three and one-half years before admission, and sanatorium care had been instituted. Following a thirty-four hour labor, a mid-forceps delivery was performed and because the placenta failed to separate, manual removal was done. Six days post-partum, the patient's temperature rose to 104.4° F. Physical examination of the chest suggested renewed activity of the tuberculous process at the right apex. For this reason, uterine and blood cultures were not taken until three days later. Sulfanilamide, in 100 grain daily doses, was started at this time. On the sixth day after the first elevation of temperature, group A, virulent hemolytic streptococci were isolated in pure culture from the uterus and the blood stream. Because of the bacteremia, the antibody content of the patient's blood was determined. It was found that the patient possessed no demonstrable antibody to her own organism. In view of this fact, together with the fact that the patient continued to be severely ill in spite of sulfanilamide therapy, immunotransfusion was advised. Three immunotransfusions were given and



sulfanilamide was continued. Seventy-two hours after the first immunotransfusion, the patient's temperature reached normal and the infection subsided. The patient made a rapid and uneventful recovery and was discharged from the hospital twenty-six days postpartum.

The chief clinical and bacteriologic findings in this last case are summarized in Table 1. Attention is called to the

TABLE 1  
(TAKEN FROM CHANDLER AND JANEWAY<sup>11</sup>)

Day of disease	Condition of patient	Sulfanilamide.		Immunotransfusions		Phagocytic titre of patient.*	No. of bacteria killed per c.c. of patient's blood.
		Dosage gm	Blood level mg	Amount c c	Phagocytic titre of donor *		
1	Onset Temperature 104.4° F						
2	Dyspnea fever prostration						
3	Condition unchanged						
4	Very septic blood culture taken	6.6					
5	No improvement	5.3					
6	Worse Oxygen tent Blood culture reported positive		7.2				
7	Condition unchanged	6.6					
8	Stuporous Blood culture taken	6.6	3.1			0-0%-25	0
9	Better after transfusion	6.6	4.4	600	44-24%-25		
10	Improving Blood culture reported negative	8.0	5.9	500	28-24%-25	61-20%-25	20,000
11	Improving	8.0	3.9	500	35-16%-25		
12	Temperature normal	8.0	6.4			254-56%-25	300,000
13	Temperature normal Soft diet.	8.0	8.3				
14	Temperature normal Out of oxygen tent	6.6	4.1				
15	Convalescing rapidly	6.6					
16	Convalescing rapidly						
17	Convalescing rapidly						

\* The first figure indicates the number of intracellular cocci counted the second figure the percentage of cells containing cocci the third figure the number of cells counted

striking response to immunotransfusion, as evidenced by the immediate rise in the phagocytic titre and the killing power of the patient's blood. It should also be noted that the content of antibody in the donors' sera, as indicated by their phagocytic titres, was not very great, and yet it was sufficient to produce excellent therapeutic results. It would appear, then,

that the use of sulfanilamide and immunotransfusion is a method of great value in the treatment of puerperal sepsis, especially in those cases in which the infection is not controlled by the administration of sulfanilamide alone.

It will be noted that in the preceding outline of treatment of streptococcal infections, reference was made only to the treatment of group A strains. There is at present very little clinical or experimental evidence regarding the susceptibility of non-group A strains to sulfanilamide. Preliminary results<sup>27</sup> on group B, C and G infections in mice seem to warrant further trial in human infections. Infections of the urinary tract with group D strains are not influenced by the drug<sup>27</sup>. Likewise, nothing is known about immune transfusion in the case of non-group A strains, but immune transfusion would theoretically be desirable in the presence of bacteremia with a low antibody titre, if an immune donor could be found.

#### SUMMARY

1 The rôle of beta hemolytic streptococci in post-abortion and puerperal infections is described and the importance of prevention in such infections is emphasized.

2 The results of sulfanilamide therapy in puerperal infections are presented.

3 The indications for the use of immune transfusion and erythrocytic antitoxin in conjunction with sulfanilamide therapy are discussed.

A portion of this material appeared in an article by C. A. Chandler and C. A. Janeway in the *American Journal of Obstetrics and Gynecology*, 38: 187, 1939.

The author wishes to express appreciation to Dr. Chester Keefer for advice in the preparation of this manuscript.

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#### DIAGNOSTIC PROCEDURES IN ALLERGIC DISEASES AND THEIR INTERPRETATION

In any given case, what is it that leads one to think of allergy in the first place? Of course, when the patient himself asks about hay fever, asthma, or mentions the hives, the train of thought starts easily. But what about the other cases with obscure headaches, with peculiar abdominal symptoms evidently of considerable severity but unexplained by any of the common clinical and laboratory examinations? What about the peculiar skin rashes, the purpuras, the erythemas and the eczemas for which there is no obvious explanation? So far, at least, we have no very direct objective method by which the question of allergy can be ruled in or out in any arbitrary fashion, but on the other hand a good deal can be done by evidence which is indirect and circumstantial, that is to say, as provided by the history. There are several points

First, the symptoms must be explained by a pathology characterized by a contraction of smooth muscle, a stimulation of glands, or an increased permeability of capillaries resulting in localized edema. Second, the clinical evidence of allergy is rarely single, for the typical patient usually has other symptoms which depend upon the same background. The nature of the abdominal pain becomes much easier to understand so soon as a few urticarial lesions appear. With the migraine may go a story of typical hay fever, either in the past or the present, and with the purpura goes perhaps a story of violent reactions when certain foods or drugs are taken. The presence of "other allergy" is one of the important criteria. Third, members of the family, either the parents or the children, may have allergy, and then finally, with allergy goes the finding of positive skin tests and the finding of an increase in the eosinophile cells in the blood. These things constitute the criteria of allergy.

Meantime, the history is all important, as said. It may be easy to show that the peculiar symptoms depend directly upon the eating of strawberries or lobster. Recurrent colds, which trouble the little boy a good deal and trouble his mother much more, may be shown to depend upon the family cat, especially if it can also be shown that the colds disappear when the boy goes away from home. But more important, the history must show that the reaction in whatever tissue is a transient temporary reaction which is quite capable of disappearing so that, in the interval, the patient has no symptoms. Kline and Young<sup>1</sup> have done well to describe the condition aptly as "reversible." The history will be discussed in greater detail later.

### SKIN TESTS

Skin tests are the exciting and dramatic part of the allergic study. They result in reactions of the immediate urticarial variety which appear within twenty minutes after the test is applied. The other kind of skin test which produces a delayed, inflammatory, tuberculin-like reaction is elicited usually by bacterial products, and although it also is called allergy, it will not be discussed here.

Immediate reactions are characterized by an urticarial wheal which develops because of the outpouring of fluid from the capillaries of the skin, so that a definite swelling is produced which increases rapidly in size, has sharply defined advancing borders, and is surrounded by a pink erythema. Such reactions develop easily when the specific substance is brought into contact with the broken skin of a sensitive individual. In most cases, the *scratch method* is quite sufficient to demonstrate a positive reaction, but sometimes the degree of sensitiveness is so slight that the more delicate *intradermal method* must be used.

With both methods, and particularly with the latter, there are technical difficulties which may interfere with proper interpretation. The intradermal test is about 100 times as delicate as the scratch test, so much so that unless great precaution is taken to keep the extracts pure, clean and quite separate from one another, chemical contamination of the different test materials occurs easily. Since Simon and I<sup>2</sup> made a study of the technic in 1935, we have learned the importance of using a separate syringe for each of the extracts to be tested, and

some authors go so far as to require that the syringes must be kept always separate and assigned permanently each to a single extract regardless of the need for washing and reesterilization in the meantime. In case the technic is good and all the apparatus is clean chemically as well as bacteriologically, the interpretation of results is not too difficult.

The recording of skin tests is important. "If the test is worth doing, it is worth recording properly." Some authors record their results by a series of plus signs or zeros. To each author, his signs mean something at that time, but will the record mean the same thing five years later? How much more accurate, how much more graphic, and how much easier to interpret, it is to have some sort of reproduction or diagram to indicate the approximate size of the wheal and erythema observed. Whether these diagrams are made by actual photograph or by tracing with blotting paper or by approximate freehand drawings makes little difference. They record what is seen and then the record can be interpreted at any time. In the great majority of cases, the skin tests are quite satisfactory. By history, the patient is sensitive to cat, to egg, or to ragweed, for example, and usually the corresponding test is positive as expected, and the other tests are negative as also should be expected. But, unfortunately, there are exceptions.

Discrepancies in the results of skin tests are common and important. They occur in two directions. First, one finds many positive tests without any symptoms to go with them. The patient has hay fever in August and September and maintains that he has no trouble in June or July, and yet it often appears that the skin test to grass pollen is often larger than the test to ragweed. Tests to orris powder, kapok, feathers, as well as to various foods, are frequently observed, and yet the patient knows he has no symptoms from any of these articles and a study of the environment shows that he is not exposed to any of them. Incidentally, positive skin tests are observed occasionally in so-called normal "non-allergic" individuals.

The reasons for these discrepancies are several, but an important one is that many positive tests represent the past history rather than the present illness. The ragweed patient has no early hay fever now, but he recalls that as a boy he did have trouble from the grasses in June and July. The woman who



uses no face powder nowadays, recalls that some years ago she had a stuffy nose and was using powder containing orris root at that time

Negative skin tests are found when the patient "ought to be" sensitive according to his clinical story. This is the other great discrepancy, and unfortunately it is not so easy to prove. However, one or two cases have suggested a possible answer. A young man began to have hay fever in early May, at the time when the tree pollens were in the air. His tests were negative, no treatment was given, and his symptoms continued until the tree pollens subsided, as shown by the symptoms of other patients. The next year, however, his tests were positive to birch and oak, and in the third year, these positive reactions were still larger. In his case, it was evident that sensitiveness had developed in the nasal mucous membrane first and in the skin later. There was a variation in the degree in which different tissues were sensitized. Possibly this finding may be correlated with the known variations in the location of sensitiveness, which variations may very well account for the fact that some people have asthma while others have hay fever, as the important symptom of pollen allergy.

This variation in the sensitiveness of different tissues may be brought out by comparative tests of different kinds made simultaneously but with the same allergens. When the scratch tests are negative, the intradermal method sometimes gives positive results. This is not uncommon. Other methods are *eye tests* in which a drop of strong extract, or sometimes a few grains of the whole pollen itself, are carefully inserted in the conjunctival sac. Another variation is the *nasal test*, accomplished in one of two ways. One can have a battery of atomizers and spray the patient's nose with increasing dilutions, noting the level at which the sneezing reaction will begin, but an easier method is this. With a flat toothpick, a small amount of pollen is held in front of the nostril and the patient is instructed to breathe in. At that moment, the toothpick is tapped and the pollen is seen to fly into the nose, where it is distributed in a more or less "normal" fashion. Such a crude nasal test is rather drastic and in our clinic is used chiefly to exclude a pollen sensitiveness, since it would seem inevitable that if such a method failed to elicit symptoms, the patient could not possibly have a clinical sensitiveness to that sub-

stance, and so corresponding treatment would obviously be useless. In a few cases, reactions have been observed in the eye or in the nose when skin tests were negative.

If now such important discrepancies in tests and symptoms exist, what right have we to lay great stress and importance upon each of the positive and negative skin tests as may be found? Is it not quite apparent that our skin tests can be interpreted only in the light of a good history, which may be amplified perhaps by whatever clinical experiments may be necessary? If the skin tests and the history will go together, that, of course, is ideal. The diagnosis is confirmed and the whole setup makes sense.

When, however, discrepancies between history and tests occur, they must be checked either by using a different method of testing, by testing the patient at another time, by reviewing the history, or by devising some sort of clinical experiment which will tend to throw that patient's test in or out of practical clinical consideration. Weak extracts, irritating extracts, dirty syringes and dull needles must all be taken into account. The proper testing of patients is not always an easy matter and the proper interpretation of any test requires a little experience and a great deal of common sense.

Incidentally, a practical point in the way of clinical experiment concerns limiting the number of substances to which the patient is exposed. For instance, the possible importance of avocado pears, nutmeg, or watercress salad can be excluded by restricting the food intake to a few simple articles chosen to give an adequate maintenance diet and a moderate variety, and yet consisting only of those foods to which the skin tests are quite negative. If the patient is no better on this "Eat Nothing But" diet, the other foods are excluded automatically. In the same way, kapok, feathers, animals, and other sources of domestic dust can be excluded by simple clinical experiment.

*Patch tests* are designed to hold the test substance in prolonged contact with the unbroken skin. Contact dermatitis is another illustration of sensitiveness localized to a particular tissue—the skin. Powders and solutions, either watery or oily in small quantity, are covered with a small square of cellophane and then held on the arm or thigh with adhesive. A positive reaction is a small reproduction of the original lesion, as in poison ivy, for example.

"*Reagins*" are antibodies of a special kind, characteristic of allergy. They are demonstrated by injecting a small quantity of the patient's blood serum into the skin of a normal recipient, and then testing the prepared sites with a dose of the specific extract injected precisely into the same spot. Advantage has been taken of these antibodies in testing by the so-called indirect method, introduced originally by Walzer.<sup>3</sup> For the child or infant who is too sick or too unruly for direct tests, his blood can be drawn, the serum separated, and then this serum injected into a series of sites in the mother's skin. In twenty-four hours, these sites in the mother are tested, the results being controlled by similar tests on her untreated skin. The method is not used in our clinic for diagnosis, although the study of reagins has given much information on the mechanism of allergy.

#### OTHER DIAGNOSTIC MEASURES

**Physical Examination.**—This is always important. Perhaps the patient's asthma is after all merely a manifestation of heart disease or of tuberculosis. Tumors of the bronchial wall can cause asthma, and we have seen a gumma of the larynx causing asthma. Such cases are rare, of course, but they may occur. Incidentally, the cause of asthma may often depend upon something wrong with the patient as a whole, and the so-called "allergist" must always and also be a doctor in every sense.

**Special Examinations.**—Special investigation is made of the nose and throat. Just as the laryngologist ought to know a little about allergy and be ready to recognize hay fever, so the internist interested in allergy should be able to look at the nose and throat. He can see the color and character of the nasal mucous membrane—whether it is pale and boggy or normal. He can see if the septum is straight and whether it is obstructive. He should be able to recognize polypi, and by a small light in the mouth, he can perform a crude transillumination which will give him a fair idea of the presence or absence of lesions in the sinuses and so can help him decide on the need for referring the patient to the laryngological expert. Hansel<sup>4</sup> has taught us to look at smears of the nasal secretion for eosinophiles, saying that in hay fever and in vasomotor rhinitis due to specific dusts, eosinophiles comprise a high pro

portion of all the cells present, whereas in infectious processes, polynuclears predominate and eosinophiles are rare

The technic of studying nasal smears is not difficult. Some of the secretion can be removed by a platinum loop, or the patient can blow his nose into the cellophane covering of a cigarette package, and then against a black background, parts of the secretion can be selected and smeared on a cover glass. After drying, the glass can be stained with Wright's stain and examined exactly like any ordinary blood stain. Sometimes such smears give very helpful information.

**The Leukopenic Index.**—In 1936, Vaughan<sup>5</sup> believed he could demonstrate that when a patient sensitive to a certain food, ate that food, the total number of leukocytes in his blood fell sharply within from thirty to sixty minutes, whereas if the same person ate other foods to which he was not sensitive, then the leukocytes tended to rise instead of fall. Even though the method is laborious and time-consuming, Vaughan believed it helped him in his diagnoses.

Other workers, however, have not been able to confirm these results. Loveless,<sup>6</sup> working in Cooke's clinic, investigated the problem with great care. She took blood smears on patients who were known to be very sensitive to foods and then persuaded them to eat small amounts of the offending substance. Blood smears were examined before and at short intervals after eating. In each case, as many as 800 white cells were counted. She found, however, that whereas some of the leukocyte curves seemed to fall off, others actually rose, and so she was bound to conclude that the method was unreliable. More promising perhaps is the recent finding of Madison and Squier<sup>7</sup> that there is a rise in the total number of eosinophiles in the blood when a person eats a food to which he is sensitive. A complete study has not been made as yet, but the experiments are on the way. Meantime, it is recalled that fifteen years ago, in 1924, Talbot<sup>8</sup> told the writer that small babies developed an increase in the number of eosinophile cells in their blood at the time of changing from breast milk to cow's milk.

**The Clinical History**—Less dramatic than objective findings but always of greater practical importance is the clinical history of the case, and on the whole it is true that with a good history one can often make a satisfactory diagnosis, while

without a good history one can accomplish but little. As described in a former article,<sup>9</sup> there are several "tricks" in the taking of an allergic history. The whole subject is of such great practical importance that it is proper to review these "tricks" here.

The first "trick" is to *use dates*. The date may be the most important fact about the onset of the original attack. How long did it last and when did it end? When came the second attack and what has happened since then? One must try to explain not only why the attack began, but also why it ended. Was there a change in residence, an intercurrent infection, an operation, or even a treatment with a good temporary result? To ask for the date will help the patient to recall the details.

The second "trick" is to *account for all the time*. If in a disease lasting five or ten years there was an interval of freedom lasting perhaps for a year or perhaps only for a few weeks or months, the fact is important and one should try to explain it.

The third "trick" is a by-product of the other two. Obviously, the systemic and chronological account of the changes, the ups and downs in the asthma, is more important than a study of details of the symptoms. Pain in the chest, the old question of difficulty in inspiration versus expiration, the matters of sneezing and of nasal obstruction, are all important, of course, but they are less important than the dates on which the various attacks began and the other dates on which they ended. If the whole story can be reviewed and set down in this way, the dates themselves will throw important light on the probable cause of trouble.

It is the history and its interpretation which constitutes the best and most important diagnostic procedure in allergic disease.

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#### CONSTITUTIONAL REACTIONS IN HAY FEVER THERAPY

THE constitutional reaction is the one great hazard in the specific treatment of hay fever. Its importance cannot be overestimated, and the understanding of its symptomatology, causes and therapy are absolutely essential to the proper management of this widespread malady. Early recognition and adequate treatment of such reactions may occasionally save life, whereas a few simple precautions may prevent their occurrence.

By constitutional reactions are meant those untoward events which occasionally follow the administration of pollen extracts, these reactions are distinct from the usual local reaction of redness and swelling at the site of injection, and they may be attributed directly to an excessive rate of absorption of the pollen extract.

#### SYMPTOMS

The symptoms are easily recognized. Cooke<sup>1</sup> has enumerated the usual symptoms as coryza, asthma, urticaria, erythema, pruritus, edema, and cough. Under infrequent symptoms he lists glandular enlargement, headache, fever, nausea, diarrhea, acute abdominal pain, dysmenorrhea, syncope, and cardiac collapse.

Burrage and Restall<sup>2</sup> reported a case in which drowsiness occurred twenty-five minutes after the dose, this was followed by coryza, twitching of the eyes, weakness, vertigo, syncope, and cramplike right upper quadrant abdominal pain. Lamson<sup>3</sup> described a case in which there was flushing of the face, athetosis, and inspiratory difficulty two to three minutes after the dose with death seven minutes later. Waldbott<sup>4</sup> reported



a case with coryza, urticaria, and dyspnea following the injected dose in thirty seconds, in the absence of a local reaction, and with death in 120 seconds in spite of the administration of epinephrine Dahl<sup>5</sup> has reported another fatality after a dose of pollen extract

Rackemann<sup>6</sup> has described three forms of general reaction The first begins with suffusion of the eyes, nose, and face, with edema and coryza, and after a few minutes, an urticaria which spreads over the whole body The second form begins with extensive redness and swelling at the site of injection, this spreads over the arm and chest and soon involves the entire body, and is followed by coryza and asthma The third form is less common and simulates the collapse of an acute abdominal emergency, with nausea, vomiting, pallor, abdominal pain, and cold moist skin

Waldbott and Ascher<sup>7</sup> reported a case in which an injection of pollen extract was followed in twenty seconds by a strange taste in the mouth, tingling around the heart, dyspnea, and collapse of such severity that the patient became pulseless and recovered only after forty-five minutes In this case no urticaria at the site of injection, or generally, was observed Walter's<sup>8</sup> patient developed sneezing attacks within ten seconds after the dose was given, and in five minutes went into shock with a systolic blood pressure of 80 millimeters of mercury, a scarcely palpable pulse, cyanosis, and asthma lasting two hours

Lamson,<sup>3</sup> in a study of sudden death associated with the injection of foreign substances, termed these conditions "anaphylaxis-like" reactions He said, "It would seem that the pattern of the anaphylaxis-like response is, in a measure at least, predetermined by the type of reaction typical to that individual"

In other words, the clinical picture of a constitutional reaction in a patient with hay fever is generally dominated by sneezing, itching of the eyes, nose and mouth, lacrimation, conjunctivitis, chemosis, nasal obstruction, and a profuse watery nasal discharge Asthma is more often part of the clinical picture in those patients who have had asthma, and so on

Our clinical experience has agreed with Lamson's The large majority of our hay fever patients with constitutional reactions have predominantly had symptoms of severe hay

fever Following the injection of pollen extract, after an interval of from five to twenty minutes, these patients have complained of itching of the face, palms, and sometimes of the whole skin, flushing of the face, and frequent paroxysms of sneezing with lacrimation and conjunctivitis, profuse watery nasal discharges, and swellings of the nasal mucous membranes, eyelids and face Local swelling, marked by itching and redness about the site of injection of from 4 to 6 inches in diameter, with occasionally erythema and edema involving the whole arm, was found frequently but was not always associated with general symptoms Asthma was a common but less frequent finding than generalized urticaria Asthma occurred more often in constitutional reactions of previously asthmatic patients Weakness, drowsiness, headache, abdominal pain, and metrorrhagia have been seen infrequently Collapse, with a low blood pressure, cold moist skin, and prostration, has been a rare finding

Cooke has stated that the severity of the symptoms in constitutional reactions is in direct proportion to the brevity of the time of onset The sooner the reaction occurs, the greater is the danger of fatal result We have found that the most distressing and alarming reactions have always occurred within a half hour of the administration of pollen extract Cooke divided constitutional reactions into the immediate and delayed forms He found that constitutional reactions which do not occur during the first hour, occur generally after an interval of from five hours to five days after the injection of the pollen extract We have found no such definite "latent period" among delayed reactions, and we would be very hesitant to consider symptoms beginning later than twenty-four hours after a pollen injection as a constitutional reaction to that treatment.

The frequency of constitutional reactions is not great Cooke and Vander Veer<sup>9</sup> reported 3.75 per cent reactions out of 4192 injections (in 339 cases) Cooke<sup>1</sup> recorded 1.9 per cent reactions out of 4291 injections (in 310 pollen cases) Furstenburg and Gay<sup>10</sup> had only 0.25 constitutional reactions out of 29,537 injections (in 532 pollen cases)

It must be borne in mind, however, that every hay fever patient receiving specific treatment is presumably a potential case of constitutional reaction

## CAUSES

The causes of these constitutional reactions are not fully understood. Some of the contributing factors, however, can be stated. Since an excessive rate of absorption of the pollen extract—that is to say, excessive for the individual in question—appears to be a necessary requirement for the production of a general reaction, it then becomes clear that the mode of introduction of the dose and the size of the dose are certain to become influential factors in this discussion.

Accidental intravenous injection is one obvious method of increasing the rate of absorption, and this factor has been considered by many authors<sup>1, 4, 7, 12, 13, 24</sup>. Presumably those constitutional reactions which develop within one or two minutes of injection are dependent upon this mechanism. Waldbott and Ascher<sup>7</sup> made the diagnosis of intravenous injection by the severity and rapidity of the development of the reaction, the failure to demonstrate a local reaction, the absence of the customary allergic symptoms, and the predominance of symptoms referable to edema in the lungs and liver. In their experience this occurred only four times in a total of 41,037 injections. In contradistinction to this, they found that in cases of inaccurate dosage there was always a time interval of several minutes, during which a more or less marked wheal arose at the site of injection, and that the symptoms which developed were allergic in nature. The cases described in the literature in which collapse has developed within five minutes may be ascribed to this mechanism or to that of backseepage from the needle puncture into a vein, as described by Waldbott and Ascher. The diagnosis of this accident was made on noting blood at the skin puncture site, followed by the development of generalized urticaria, with or without collapse, in from one to five minutes. The diagnosis of backseepage into a vein was made thirty-seven times in this same group of 41,037 injections. The cases reported by Walter,<sup>8</sup> Lamson,<sup>3</sup> Waldbott,<sup>4</sup> and Joyce<sup>11</sup> could be well explained on the basis of accidental intravenous administration or backseepage into a vein.

We have not observed cases which would fall into either of these diagnostic categories, and we assume that they must be rare. We can only comment that we have observed the absence of local reactions repeatedly in the presence of con

stitutional reactions, and furthermore that blood has frequently been noted at the site of skin puncture after pollen injections without the advent of further untoward events

An overdose of pollen extract is undoubtedly a major factor in causing most constitutional reactions. Occasionally this occurs on the first dose of a course of treatment, but due caution in selection of the first dose will make such an event unusual. Too great an increase over previous dosage is a cause which can sometimes be avoided. The change from old to new extracts has also been blamed for trouble in the past, but if fresh extracts, not more than two months old, are stocked regularly during treatment, then such difficulties should be overcome. Mistakes in measuring the proper dose in the syringe, or from taking the dose from the wrong bottle, account for a few general reactions. A realization of the possible serious consequences of such mistakes should do much to reduce them to a minimum.

A change in the dilution of the extract injected (from a larger volume of weaker, to a smaller volume of stronger solution) has been considered to be an important factor in causing general reactions. Cooke, Duke,<sup>12</sup> and Furstenburg and Gay<sup>10</sup> have mentioned this point. It is our opinion that if extracts are made and diluted with care, such a difficulty should not be encountered. We do not believe that the differences in volume, being customarily in the range of fractions of 1 or 2 c c, should affect the rate of absorption to an extent of importance in this regard. It is to be remembered that when a change of dilution of material is made, the actual dose is often increased at the same time. We have observed general reactions coincident with changes in volume and concentration of the extracts used, but these cases have been in the minority and even in them we did not feel that the changes in dilution could be held clearly responsible for the reactions. With the beginning of the period of pollination, the patient begins to inhale pollen and, at that time, overdosage is very likely to occur. In this way, the taking of doses from two sources, inhalation and injection, at the same time may explain untoward reactions following treatment doses. Duke, on the other hand, has advised the reduction of all doses to a constant volume with physiologic solution of sodium chloride.

Another contributing factor alluded to above is the possible summation of the dose with homologous antigen from some other source, such as the inhalation of pollen during the pollen season. Summation may also occur with pollen extract injected during the previous thirty-six hours, according to Walzer<sup>13</sup> who advises that the intervals between doses be from four to seven days to avoid such a contingency. Summation of the dose, with exposure of the patient to other foreign substances to which he is hypersensitive, has been suggested by Cooke and by Waldbott as a possible cause of some general reactions. However, the experimental work of Pratt<sup>14</sup> with multiply sensitive guinea-pigs may be regarded as evidence against the probability of this hypothesis.

Similar anaphylaxis-like phenomena occurring after the injection of foreign substances other than pollen extracts have been described by Rackemann,<sup>15</sup> Cooke,<sup>1</sup> Lamson,<sup>3</sup> Lowens,<sup>16</sup> Tuft,<sup>17</sup> Robinson,<sup>18</sup> Gelfand,<sup>19</sup> and by many others. The similarity in symptomatology suggests a common mechanism in their production.

#### A STUDY OF 100 CONSTITUTIONAL REACTIONS

We have studied 100 constitutional reactions occurring in the Allergy Clinic of the Massachusetts General Hospital and in private practice during the course of treatment for hay fever of forty patients. This includes thirty-three general reactions following treatment with grass and sixty-seven general reactions following treatment with ragweed extracts. Table I shows the small number of reactions which were associated with a change in dilution of the extract used.

TABLE 1  
CONSTITUTIONAL REACTIONS IN HAY FEVER PATIENTS

	<i>Reactions</i>
After first dose	7
After dose with change to stronger dilution	26
After increased dose without change in strength of extract	67
Total	100

In Table 2 is shown the relation between the size of the local reaction and the occurrence of general reactions.

TABLE 2  
SIZE OF LOCAL REACTION ACCOMPANYING GENERAL REACTION

	Number of general reactions.	Size of local reaction.				
		Marked	Moderate	Small	None	>
Cooke <sup>1</sup>	83	24	5	4	5	45
Greene	100	43	20	11	3	23
Total	183	67	25	15	8	68

Table 2 indicates that while the local reactions under consideration most commonly were large, they were frequently moderate or small and occasionally even absent. In this series, any local reaction of erythema and induration of 2 inches or more in diameter was considered a marked reaction. A local reaction 1 inch or less in diameter was considered a small reaction.

An attempt was made to correlate reactions to serial dilution scratch tests with the dose which precipitated the general reaction. It was found that on twenty-three occasions a constitutional reaction followed a dose of 0.4 cc or less of the weakest dilution giving a positive skin reaction (erythema 2 cm in diameter or more). On sixty-nine occasions, however, the constitutional reaction occurred on a dose of stronger material.

It was found in sixty-two instances that the patient was able to tolerate a larger dose than that followed by a general reaction later in the season without any such difficulty. In thirty instances the patient did not receive larger doses later.

The amount of pollen extract constituting an overdose is dependent upon the so-called tolerance or grade of sensitiveness of the patient. This tolerance varies widely in different patients and is a conditioning cause of constitutional reactions. The tolerance becomes altered during the course of treatment in some patients, while in others it appears to be relatively fixed, so that equal doses are followed by a constitutional reaction on repeated occasions. If it is possible to raise a patient's tolerance to pollen extract subcutaneously, then it would seem likely that his tolerance to pollen in the air would be

raised by the same procedure and that the treatment would be beneficial. On the other hand, if a patient's tolerance to pollen extract subcutaneously is not altered by or during the course of injections, then it would appear likely that the treatment would not result in increased tolerance to pollen in the air. Table 3 represents an attempt to test these concepts. The results of treatment are recorded according to the statement of the patient at the close of the season.

TABLE 3  
RESULTS OF TREATMENT FOR HAY FEVER

	Perfect or nearly perfect	Good relief	Slight relief	No relief
Seasons treatment in which a dose greater than that causing general reaction was reached	15	26	3	5
Seasons treatment in which a dose greater than that causing general reaction was not reached	3	13	5	3
Total	18	39	8	8

We have been unable to find any definite relationship between the level of dosage producing general reactions and the severity of the patient's hay fever, or the results of treatment (as judged by the patient's estimate at the end of the season).

The effect of constitutional reactions on the hay fever was thought by Cooke and Vander Veer to decrease the susceptibility to the protein and to be therefore ultimately advantageous. Joltrain<sup>20</sup> reported a case of hay fever in which the occurrence of a general reaction during the course of treatment was followed by complete relief of symptoms for the remainder of the season and for several years following. We have observed no such happy event. We have found that serial dilution skin tests done at the end of the season, after a constitutional reaction, showed greater skin sensitiveness in nine cases, no change in forty-two cases, and definitely smaller skin tests in eighteen cases. The changes in skin sensitiveness do not, however, necessarily indicate a parallel change in clinical sensitiveness, and skin tests may remain unchanged in size in patients whose clinical sensitiveness becomes decreased.

## PROPHYLAXIS

The prevention of general reactions requires several precautions. Skin tests done before starting treatment should be scratch tests with the dilutions of pollen extract with which one intends to treat the patient. The weakest dilution should be no stronger than 1:5000 (200 Noon units per c.c.). Treatment should be started with 0.1 c.c. of the strongest dilution which gives a completely negative scratch test. If the weakest material gives a positive test, then the dose should be 0.05 c.c. of the weakest material, or else it should be diluted further. These measures limit reactions after the first dose to a minimum.

The doses should be given at four to seven day intervals, increasing the size of the dose only if the local reaction produced by the preceding injection was less than 2 inches in diameter, and never increasing by more than doubling the preceding dose. Observation by the patient of the local reactions (occurring from one to four hours after the injection) should be well worth the trouble it costs him.

Table 2 has emphasized the fact that marked local reactions occurred with more than half the general reactions in which they were noted. It would therefore seem that the local reaction is a fairly reliable warning signal in many cases.

Satisfactory local reactions should be produced in a fairly uniform manner if  $\frac{1}{8}$  inch, 26 gauge hypodermic needles are used for all treatment injections, introducing the needle point at an angle of approximately 45 degrees to the skin of the arm. A relatively avascular site, such as the region of the deltoid insertion, should be chosen when possible and the plunger of the syringe should always be withdrawn before injecting the dose, in order to be certain that an intravenous dose is not given.

Changes in the size of the dose must be made with care, as has been indicated, and during the pollen season such changes must be made with the greatest caution. It must be recalled that pollen in the air may add to the extract given subcutaneously, to produce an increase in the severity of a patient's hay fever. Consequently, at such a time, an increase in the dose should be a small one, and it is often wise to keep the dose constant during the season. Sometimes it is helpful to make drastic reduction in the size of doses during the pollen



season as indicated by the patient's symptoms. Whenever a patient has had a general reaction following a given dose, the next dose should always be smaller, and subsequent increases must be made with care. This is particularly true when several such reactions have occurred at about the same dose in the same patient. Care should be used in approaching doses which have been followed by constitutional reactions in former years of treatment. Whenever a general reaction is feared because of previous trouble with such a dose, or because of a large local reaction, it is wise to have the patient wait for twenty minutes after his dose.

More active preventive measures have not seemed worth while to us. Duke<sup>12</sup> has recommended reducing all doses to a constant volume, and mixing pollen extracts with epinephrine and ephedrine, and the frequent application and loosening of a tourniquet above the site of injection for at least five minutes after the dose is given. The studies of Feinberg and Bernstein<sup>21</sup> have indicated that ephedrine is not very effective in decreasing the tide of absorption of the pollen extract and that the action of epinephrine is chiefly to delay, rather than to decrease it. It would appear that delay in the onset of constitutional reactions was not to be desired. We have avoided serious mishaps without the use of the tourniquet after every injection, although the danger of accidental intravenous administration could certainly be diminished by this measure. Injections of pollen extracts may be given subcuticularly (Duke), intradermally, subcutaneously, or intramuscularly. Duke and Waldbott<sup>12, 4</sup> have recommended the injection of a very small fraction of the total dose first, to be sure that the total dose was not given intravenously. We have used the subcutaneous route without this precaution.

#### TREATMENT

The treatment of constitutional reactions has been described by Cooke. He recommends the use of a tourniquet above the site of injection, epinephrine (1:1000) in doses of 1 c.c. in adults and 0.4 to 0.6 c.c. in children, is given at once subcutaneously, and intravenously if the reaction is severe, and is repeated at intervals of from two to five minutes. If the symptoms continue to increase in the presence of cardiac dilatation, strophanthin (1 mg. intravenously) followed by an appropriate dose of morphine is advised.

We have generally found epinephrine, 1 1000, effective in subcutaneous doses of from 0.30 to 0.60 c.c. repeated at ten to fifteen minute intervals if necessary. We have not encountered cases wherein the use of strophanthin was needed, and we should hesitate to give morphine in such a situation because of the possibility of idiosyncrasy to that drug.

Insley<sup>22</sup> has recommended the substitution of a blood pressure cuff for the tourniquet, maintaining the pressure at 120 mm. of mercury for two minutes and then dropping it to 80 mm. and then to 60 with subsequent variations in pressure according to the symptoms over the next thirty to sixty minutes as required. He found that the effect of cutting off the venous and lymphatic flow in this manner was felt in from thirty to sixty seconds after the application.

Intravenous and even intracardiac injections of epinephrine may be required in the most alarming cases. Joyce<sup>11</sup> described a case in which a dose of pollen extract was followed by asthma, cyanosis, bubbling râles, dyspnea, failing pulse, and unconsciousness in rapid succession. Three 1 c.c. doses of epinephrine (1 1000) were given at five minute intervals by the intracardiac route. Artificial respiration, intravenous sodium chloride solution and morphine sulfate, grain  $\frac{1}{8}$ , were given, with gradual subsidence of symptoms in the course of thirty-six hours.

We recommend the use of intravenous glucose (500 c.c. of 10 per cent solution in saline) to combat any tendency to shock. One cubic centimeter of epinephrine (1 1000) may be mixed with this solution. Rice<sup>23</sup> has described the use of epinephrine and the blood pressure cuff in a patient under treatment for hay fever who received a gross overdose by mistake. This patient developed hay fever and urticaria which subsided in four hours.

Ephedrine solution, in doses of  $\frac{3}{8}$  to  $\frac{3}{4}$  gram, either alone or combined with amytal (grain  $\frac{3}{4}$ ), is often helpful in the treatment of delayed reactions beginning over an hour after the treatment injection, it is not effective, however, in the severe reactions encountered within the first half hour.

#### SUMMARY

- 1 The constitutional reaction presents a grave hazard in the treatment of hay fever. These reactions attributable to such treatment have been recorded in the literature.

2 Recognition of the symptoms is required for prompt and effective treatment Symptoms of hay fever are prominent, as urticaria and asthma are frequently present

3 An analysis of 100 cases shows that most of the reactions are not to be blamed upon changes in dilution of the extract used A constitutional reaction is usually, but not always, accompanied by a marked local reaction Those patients in whom it was possible to increase the dose above the level at which a general reaction occurred, received the maximum benefit from the treatment

4 General reactions may be prevented by proper use and interpretation of skin tests before treatment, by attention to local reactions, and by cautiously increasing the doses to quantities which have been previously associated with constitutional reactions The treatment of constitutional reactions consists in the use of epinephrine and the tourniquet or blood pressure cuff for the immediate reactions Ephedrine sulfate may be sufficient to control symptoms of delayed reactions

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### TREATMENT OF AMOEBIASIS

**Preliminary Remarks**—Before undertaking the treatment of a case of amoebiasis, the diagnosis should have been confirmed by demonstrating the presence of the parasite, *Entamoeba histolytica*. It should be borne in mind, on the one hand, that absence of recognizable symptoms does not prove absence of serious pathology and, on the other hand, that the presence of vague digestive disorders or of symptoms of debility does not justify the assumption, without reservation, that the amoeba is the cause of them. In all cases of amoebiasis, complete eradication of the parasite is the goal.

#### MILD OR SYMPTOMLESS CASES

When symptoms are lacking or have consisted only of slight diarrhoea and other mild digestive disorders, it is not necessary that the patient remain in bed. He may be allowed, while under treatment, to continue his usual activities provided that fatigue and chilling can be avoided. Even so, foods which have disagreed with the patient should not be taken, and alcoholic beverages should be prohibited until recovery is complete.

Therapy should be initiated with one of the less poisonous drugs. Probably the safest of these is chiniofon powder\*. Essentially similar preparations are sold under the trade names of "Yatren," "Anayodin," and "Loretin."

**Chiniofon**.—Long and extensive experience with chiniofon by many observers has shown that, although it causes diarrhoea in some cases, it is a remarkably safe remedy when

\* "A mixture of 7-iodo-8-hydroxy-quinoline-5-sulfonic acid, sodium bicarbonate and sodium iodohydroxyquinolinesulfonate, containing not less than 26.5 and not more than 28.9 per cent of iodine (I)." (United States Pharmacopoeia. See also N.N.R. Amer. Med. Assoc., Chicago, 1933, p. 173.)

given by mouth or by rectum in the usual therapeutic dosage. Chiniofon should never be administered intravenously because deaths have resulted from its use in this manner. Rarely, symptoms of hyperthyroidism have been attributed to the use of chiniofon. When hyperthyroidism is present, the iodine content of chiniofon should be taken into consideration. Caution in the use of chiniofon is advisable, also, when there is disease of the liver. An interval of ten days should elapse before giving a second course of chiniofon.

The usual dosage of chiniofon is 3 to 4 pills or tablets administered three times daily for eight to ten days. Each pill or tablet contains 0.25 gm (4 grains) of chiniofon. Enteric coated pills are required because chiniofon is destroyed by gastric juice (Bastedo, 1937).

Craig (1934) recommended chiniofon highly for the milder types of amoebiasis. My own less extensive experience with this drug is comparable. Chiniofon frequently causes a mild diarrhoea, but its use need not be discontinued unless the diarrhoea should become severe.

**Carbarsone**—As an alternative drug, carbarsone\* is to be recommended highly. Reed (1934), and his associates, have used it extensively. I have found it satisfactory, and Hakanson (1938) has recently reported favorably upon it. In spite of the arsenic content of carbarsone, few serious toxic effects have been observed following its use. Occasionally, cutaneous lesions and other toxic manifestations, such as occur in arsenical poisoning, have occurred. The chemical structure of carbarsone suggests that it might damage the optic nerve. Very rarely, visual disturbances have occurred. It is therefore important that this possibility should be borne in mind. Like other arsenicals, carbarsone should be used with caution, if at all, in the presence of disease of the liver or of the kidneys. Excretion is relatively slow, so that it would seem wise not to undertake a second course of treatment with carbarsone until after an interval of two weeks or more.

The usual dose of carbarsone for an adult is 0.25 gm (4 grains) administered by mouth twice daily for ten days in tablet form.

\* p-Carbamido-phenylarsonic acid, p-Carbamido-benzenearsonic acid. Carbarsone contains from 28.1 to 28.8 per cent arsenic (As). (N. R. Amer. Med. Assoc., Chicago, 1938, p. 100.)

After a course of treatment with chiniofon or with carbarsone, the stools should be examined for amoebae and for cysts of *E. histolytica* at intervals of a week, for four weeks, and at intervals of a month thereafter, for three months or more. When infestation persists, a second course of treatment should be instituted either with the same or with another drug. No known drug is uniformly effective in all cases.

**Acetarzone**—Another arsenical which has given good service for many years in the treatment of amoebiasis is acetarzone, which is known also under the trade name of "stovarsol." It contains 27.1 to 27.4 per cent of arsenic (N.N.R. 1938, p. 99).

Signs of arsenical intoxication resulting from the use of acetarzone appear to be decidedly more frequent than when carbarsone is employed, and it is therefore being used less and less. The usual dose of acetarzone for an adult is 0.25 gm (4 grains) two or three times daily for seven days, in tablet form by mouth.

**Vioform**.—This is a non-arsenical preparation which is chemically allied to chiniofon. It contains more iodine than does chiniofon and it may prove to be even more valuable. Having been introduced comparatively recently, it has not yet been very widely used. Vioform occasionally causes gastrointestinal irritation. Probably it should be used with caution in hyperthyroidism and in the presence of disease of the liver.

Vioform-Ciba (N.N.R. 1938, pp. 260–261) is iodochlorohydroxyquinoline. The dosage of vioform recommended for an adult is 0.25 gm (4 grains) of the powder in a capsule, one such capsule to be administered three or four times daily for ten days. The course of treatment may be repeated after an interval of ten days (David *et al.*, 1933).

#### AMOEbic ENTERITIS

Amoebic enteritis without visible blood in the stools may be acute, chronic, or recurring. The milder cases usually respond promptly to treatment as advised for mild or symptomless cases of amoebiasis. When diarrhoea or other gastrointestinal symptoms are distressing, or when the temperature is at all elevated, the patient should remain in bed and should take a non-irritating diet which leaves little residue in the intestine. These restrictions should be continued until the stools



have become normal or nearly normal in appearance. Alcoholic beverages must be debarred while treatment is in progress and they should be avoided for several months or until all danger of relapse has passed. Medication as advised above for mild or symptomless cases is usually adequate.

#### AMOEBIIC DYSENTERY

When blood and mucus are visible in the stools, the term "dysentery" is applicable. Slight fever may be present. The symptoms may develop early in the infestation, or they may represent an acute exacerbation of a chronic process. In cases of long duration, the ulcerative process in the intestine may have led to extensive fibrosis and thickening of the intestinal wall or to the formation of ulcers with undermined edges in which secondary infection with various kinds of organisms is aggravating the process. So long as the dysentery lasts, the patient should remain in bed.

**Diet**—The diet should consist of liquids only for a few days. Thereafter, the food taken should be easily assimilable, nutritious, and such as to leave a non-irritating residue of no great bulk in the intestine. Maintenance of the best possible nutrition is important, and the diet should contain an abundance of the various vitamins. Unless symptoms are urgent or alarming, treatment as advised above for mild or symptomless cases is recommended.

**Emetine**.—The most effective drug for controlling the acute symptoms of amoebiasis is emetine. Unfortunately, it must be used with caution to avoid the symptoms of intolerance which not infrequently result from its use. Emetine is more effective when the contents of the gastro-intestinal tract are alkaline than when they are acid.

Emetine is irritant to mucous membranes and therefore unsuitable for rectal administration, but it can generally be injected parenterally without causing discomfort. Craig (1934) recommended its use subcutaneously, but Manson-Bahr (1939) and Chopra (1936) prefer the intramuscular route. Absorption of emetine is rapid but elimination is very slow. The effects therefore tend to be cumulative. After parenteral injection, emetine is excreted by the gastro-intestinal tract, by the kidneys, and apparently also into the bile by the liver.

Emetine destroys *E. histolytica* when in the intestinal wall,

but has little effect upon amoebae in the lumen of the bowel and still less, if any, effect upon cysts

It is believed that emetine, even in therapeutic doses, can cause parenchymatous degeneration of the heart muscle which may result in death or in permanent impairment of the cardiac function. Without warning, a marked fall of systolic blood-pressure, tachycardia, weakness of the pulse, arrhythmia, dyspnoea, or circulatory collapse may appear during or after a course of treatment with emetine. These toxic symptoms may first appear after an interval of a few days or after a longer period, the interval depending, perhaps, upon the time when the patient resumes activity.

In persons who are unusually susceptible to emetine, Chopra (1936) has observed urticaria and dermatitis. I have seen circulatory signs of intolerance after three days of treatment with the usual dosage (3 grains).

Another group of untoward effects which have been attributed to the use of emetine are characterized by extreme muscular weakness in the extremities, signs of motor polyneuritis, or bulbar symptoms referable to the nerves of the medulla. These signs may first appear soon after completion of the course of treatment with emetine, or they may develop after a considerable interval. Death may result. Inasmuch as beriberi and pellagra are recognized now as frequent concomitants or sequelae of gastro-intestinal disorders, it seems possible that some of the neurological symptoms which have been attributed to emetine may have been caused by B-avitaminosis. Nevertheless, the use of emetine should, probably, be discontinued whenever neurological symptoms appear.

The gastro-intestinal symptoms ascribable to emetine, when used parenterally, may be mild or severe. They include diarrhoea, which is usually slight and, rarely, nausea or vomiting. Slight diarrhoea does not require discontinuance of the treatment with emetine, but reduction of dosage may be advisable.

Not infrequently, emetine causes marked mental depression. Its use may be followed by branny desquamation of the skin and an atrophic condition of the nails (Manson-Bahr, 1939).

Emetine is generally employed in the form of hydrochloride, of which the usual dose for an adult is 0.032 gm ( $\frac{1}{2}$  grain) administered subcutaneously or intramuscularly twice

daily for a period of from five to ten days. There is no advantage in or justification for giving emetine intravenously. To do so is needlessly to endanger the life of the patient.

Emetine should be used only to control severe or alarming symptoms of amoebiasis. These symptoms having been controlled, the use of emetine should be discontinued at once. When so used, emetine will seldom be needed for more than five days. To continue its use for more than ten days is to incur grave risk to the patient. *Because excretion is slow*, a second course of emetine should not be given, if at all, until after an interval of *at least four weeks*.

In order to minimize the risk of circulatory failure, a patient who is receiving emetine should be confined strictly to bed, and the pulse rate and the blood pressure should be recorded twice daily. Should any circulatory disorder develop, the emetine should be discontinued at once.

After a patient has been treated with emetine, activity should be resumed very gradually, and the condition of the circulation should be closely watched. Younger persons, except young children, tolerate emetine better than do the elderly. Pregnancy is not disturbed by emetine.

Emetine is contraindicated when there is debility, myocardial weakness, nephritis, or disease of the liver other than that of amoebic origin. Surgical intervention is so dangerous after the use of emetine that the drug should be avoided in cases which may require a severe surgical operation.

In order to complete the cure of severe amoebic dysentery, it is necessary to follow the course of emetine with one or more courses of treatment with some other drug.

#### CHRONIC DYSENTERY

In the more chronic or obstinate cases, a course of treatment with chiniofon or carbarsone may be supplemented to advantage by the use of retention enemata of chiniofon or of carbarsone administered occasionally or for a few consecutive days. For this purpose, 1 to 5 gm (15 to 75 grains) of chiniofon dissolved in 200 c c of warm water, or 2 gm (30 grains) of carbarsone dissolved in 200 c c of a 2 per cent solution of sodium bicarbonate, can be recommended. Meanwhile, use of these drugs by mouth should be discontinued or the dosage should be correspondingly reduced.

Deeks' treatment (1913) is an excellent alternative or supplementary method for the treatment of intestinal amoebiasis in any stage except when the severity of symptoms requires the use of emetine. The Deeks method usually causes complete disappearance of amoebae and cysts within a few days and it promotes the healing of ulcers in the intestine. A second course of treatment with bismuth may be required to complete the cure. The treatment is as follows:

1. A preliminary dose of castor oil

2. Rest in bed

3. A generous milk diet, except that for a few days during the acute attack, when plain fruit juice may be given once or twice daily instead of milk.

4. Irrigation of the bowel with saline solution or plain water from one to three times daily

5. Administration of heroic doses of bismuth subnitrate: a heaping teaspoonful (equivalent to about 180 grains by weight, or about 12 gm.), suspended mechanically in almost a tumbler full of water, or preferably effervescent water, every three hours, night and day in severe cases. Suspension of the bismuth in a sufficient amount of fluid is essential to prevent the bismuth from forming a paste. After the number of stools has decreased and the tongue has become clean, 3 or 4 doses of bismuth daily are sufficient. In very chronic cases, one or two doses of bismuth should be taken daily for from six weeks to six months after convalescence has become established.

6. The strict milk diet should be continued until the tongue clears, tenderness over the bowel has disappeared, normal elasticity of the skin of the abdominal wall has been regained, and the number of stools has been reduced to one in twenty-four to forty-eight hours. Thereafter, a normal diet should be resumed gradually.

In a subsequent article by James and Deeks (1925), it was said that the bismuth might be administered in milk, and the view was expressed that saline irrigations are needed only when there are ulcerative lesions near the rectum, and tenesmus. It was further advised that, when tenesmus or abdominal distress are severe, hypodermic injections of morphine and atropine may be employed for relief at the outset. They should not be given as a routine.

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The Deeks method, to be successful, must be applied under

conditions of strict control. It can be recommended particularly for severe or chronic cases in which the condition of the patient requires treatment in bed.

The use of these large doses of bismuth subnitrate occasionally leads to the development of cyanosis through the appearance of methemoglobin in the blood. This effect is attributable to the formation of nitrite in the intestine. Use of the subnitrate should be discontinued when methemoglobinemia occurs and the subcarbonate should be administered in its stead.

Probably on this account, some physicians have preferred the subcarbonate ("carbonate") to the subnitrate (Chopra, 1936, pp 369-370). They seem to have used it, however, in relatively small doses and there is insufficient evidence upon which to base a comparison of the relative efficacy of the two drugs. It seems likely, however, that the subcarbonate is as effective as the subnitrate.

Manson-Bahr (1939, pp 192-195) still recommends the intensive use of emetine bismuthous iodide ("E B I"), B P 1932, for cases of amoebiasis requiring treatment in bed, in spite of the fact that use of this drug is trying to the patient and that toxic effects may occur. My own experience leads me to believe that bismuth is equally effective and less objectionable.

Many other drugs have been used for the treatment of amoebiasis but, in the present state of knowledge, no one of them seems to have special advantages.

#### COMPLICATIONS

*Acute amoebic hepatitis* generally yields promptly to treatment with emetine as previously described.

*Abscess of the Liver*—Treatment with emetine may suffice, but a large abscess should be drained. The trochar and cannula should be used first, but a Potain aspirator may be needed. Should the pus obtained show the presence of streptococci or other virulent bacteria, open surgical drainage becomes necessary.

*Acute emergencies*, such as acute appendicitis, perforation, intestinal obstruction, and severe hemorrhage, are rare. They should be recognized promptly and treated surgically.

*Chronic appendicitis*, or signs simulating it, may depend

upon amoebic lesions of the appendix and may yield to the usual treatment for amoebiasis. Therefore, in cases which are not urgent, operation should be deferred until the effect of medicinal treatment has been ascertained.

*Abscess of the lung* requires much the same treatment as does abscess of the liver.

*Abscess of the brain* has rarely, if ever, been treated with success.

*Concomitant diseases*, e.g., avitaminosis, bacillary dysentery, and cancer of the intestine, require modification of treatment. Pseudopolyposis or granuloma of amoebic origin may easily be mistaken for cancer (Gunn and Howard, 1931, and Anderson *et al*, 1936).

*Reinfection* from carriers within the home is, probably, an important factor in certain cases—which treatment seems to have failed to eradicate the parasite (David *et al*, 1933).

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BOSTON

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### DIAGNOSIS AND TREATMENT OF FUNGOUS INFECTIONS OF THE SKIN

IN the diagnosis of fungous infections of the skin, a principle of great importance and one worth stressing at the start is complete examination of the skin. The morphology of fungous infections varies considerably and is more often atypical than classical. The presenting complaint is commonly in reference to a lesion which attracts attention because of itching or its conspicuous location and the patient may not be aware of all areas of involvement. The appearance of such a lesion may not arouse suspicion of fungous infection until collateral evidence is obtained by careful inspection of the feet, groins, anal region and armpits. The finding of significant foci on the feet may lead to mycological studies and proved diagnosis.

It seems that, in the practice of medicine, diseases of the skin appear much less often in classical form than they do in more or less atypical varieties, and the moment a skin disease becomes atypical, difficulty arises. This confusion often disappears when the patient undresses completely and is carefully inspected from scalp to feet. Other areas of involvement are then found, often unknown to the patient, and some of these may possess diagnostic features which are lacking in the area representing the presenting complaint. The patient's denial of involvement of areas not open to ready inspection is often misleading, and his opinion regarding the status of his scalp or feet is often worthless.

Frequently, patients are unaware of foci of dermatophytosis involving the interdigital spaces of the feet, and after the patient has so denied the existence of any scaling or fissuring between the toes, one may be quite surprised to find even quite

severe evidence of a fungous infection. Many people never wash carefully between the toes and never actually inspect these areas. Having never noticed itching of the feet, they are therefore led to conclude that they do not suffer from "athlete's foot." It is a common misconception among the laity that "athlete's foot" is uniformly a severe disturbance always associated with itching. Actually, a very substantial percentage of fungous infections are associated with no itching at all.

Positive dermatological findings unknown to the patient may turn up not only on the feet, but also in the axillae, groins and perianal region, all of which are common fields for the activity of fungous infections.

The morphology and distribution of fungous infections involve a few outstanding concepts so widely understood as to merit only casual mention. Though fungi tend to seek warm moist areas, such as the flexural surfaces of elbows and knees, umbilicus, groins, intergluteal fold, post-auricular regions, interdigital spaces and axillae, actually they can invade any area of the skin. Sharp margination of the individual lesion is a helpful aid in diagnosis, but is not by any means a constant feature. The typical primary lesion begins as a small lesion characterized by varying changes, such as erythema, vesicle, or papule, and spreads by peripheral extension with a slightly raised oval or circinate border, usually sharply outlined. The classical lesion shows central clearing along with peripheral spread. Often the red ring-shaped border stands out in contrast with the white scaly center.

These classical morphologic features may characterize the mycotic lesion in any locality, but on very moist intertriginous surfaces the picture of dermatophytosis tends more toward the formation of solid plaques of erythema, edema, maceration, lichenification, and scaling.

The morphologic changes produced in the skin by mycotic infections vary considerably from the usual familiar classical pictures. The appearance may be that of a mild nondescript superficial scaliness, or it may progress to granuloma formation and ulceration. Between these extremes one finds many intermediary variations.

The pathologic physiology of fungous infections involves, in light of modern knowledge, just a few fundamental con-

cepts These are well worth reviewing from the standpoint of both diagnosis and treatment

It is well recognized that the human skin bears an habitual flora of living bacteria, fungi, and yeast cells It is probable that in a high percentage of the general population, pathogenic fungi are carried constantly upon the skin, with or without clinical manifestations of disease Pathogenic fungi, such as *Epidermophyton*, *Trichophyton interdigitale* and *Monilia albicans*, occur frequently as quiescent inhabitants of the human skin

The skin's resistance to these fungi is regulated by a delicate mechanism which is easily upset Adequate local immunity may be lowered rapidly by minor systemic disturbances and by various local skin irritants Complete and permanent sterilization of the skin and nails of infected or carrier individuals is beyond the present powers of medical science All cases probably carry their own source of reinfection, thus explaining the recurrent nature of fungous diseases

As a rule, the most common pathogenic fungi have the property of multiplying only in the dead portion of the skin, including the horny layer of the epidermis and hair follicles, the hairs and nails Apparently they can survive but cannot propagate in living tissues This simple biological conception explains the chief phenomena displayed by these infections The disease remains localized in the majority of cases, although it undergoes systemic spread in occasional cases Rarely, fungi have been found in the blood and lymph nodes, but it is unlikely that they are capable of multiplying within internal organs

Since fungi flourish only in dead, keratinized material, they will grow along a hair only to the neck of the bulb At this level, the cells of the bulb are undergoing cornification and provide a suitable culture medium Below this level, however, the fungus is incapable of extending because it cannot invade the living cells The microorganism, however, will reinfect constantly the newly formed keratin and the process is perpetuated chronically in this way at the neck of the bulb

Of the many manifestations of fungous infections, there is no more important group than that commonly involving the hands and feet and usually referred to by the terms "dermatophytosis" and "dermatophytid" The organisms usually en-

countered in this group include Epidermophytos, Trichophytos and Monilias. In reference to diagnosis in this group of fungous infections of the hands and feet and the associated "ids," it is not always possible to differentiate sharply between the morphologic changes attributable to the fungus and the changes which can be caused by contact allergens and external chemical irritants of various types. Fungous infections will lead to scaling, vesicle formation and eczematous reactions, but soap, wool and mercury, for example, acting externally, may produce very similar skin changes. It is important also to remember that fungous infections and contact dermatitis often run hand in hand and there is definite etiologic interplay between these two diseases. Chemical irritation of many types lowers the resistance of the skin to invasion by fungous infections. The existence of fungous disease of the feet probably increases the ease with which the hands explode cutaneously upon contact with such things as torch oil,<sup>1</sup> soap and wool.

The laboratory procedures of importance in the study of fungous infections include direct microscopic examination of material digested in a 20 per cent solution of potassium hydroxide, cultural studies, and identification of the distinctive fluorescence of various fungi by means of filtered ultraviolet light. These methods of investigation may be applied to hair, nails, tissues, and occasionally to wearing apparel such as shoes, caps and jock-straps.

#### ILLUSTRATIVE CASES

A case with morphologic findings not strongly suggestive of a fungous infection, but with collateral clinical evidence pointing to this diagnosis and with laboratory proof of this diagnosis, is as follows:

**Case I**—Mrs P, a woman of thirty-four years, developed in January, 1939, a patch of scaliness on the inner aspect of the left thigh. Examination a few days after the onset revealed on the lower inner aspect of the left thigh a bizarre, ill-defined patch of scaliness running in curved lines, interspaced with normal skin and with no very clear cut margination. The appearance was not decidedly characteristic of anything but was more suggestive of a winter dryness type of condition than of a fungous infection.

Examination of the feet disclosed a well-marked interdigital scaling type of dermatophytosis. This was known to have been present for a number of years and had resisted many types of fungicidal therapy. A sample of scales

was removed from the left thigh and was subjected to mycologic studies. Direct microscopic examination showed abundant, branching mycelial threads. Cultural studies were negative.

The diagnosis of fungous infection of the left thigh was thus clearly established. The manner of transmission was probably by way of the bath towel. Each bath towel was used, admittedly, on several successive days before going to the laundry. Furthermore, the bath towel was commonly used on the feet before using it on other parts of the body. The mechanism of spread from the feet thus seems obvious.

In treatment, prompt clearing of the thigh took place following three treatments with ultraviolet light and local applications of a 3 per cent alcoholic solution of iodine.

*Microsporon lanosum* is a very common cause of ringworm of the scalp, usually referred to as the "animal" type in contrast to the "human" type which is caused by *Microsporon audouinii*. *Microsporon lanosum* infection of the scalp usually responds well to rather simple forms of treatment and rarely requires the use of x-ray epilation. *Microsporon audouinii*, on the other hand, causes a much more difficult type of scalp infection and nearly always requires x-ray epilation.

The following report represents a study of a family extensively infected with *Microsporon lanosum*.

**Case II.**—A family of four sought advice in September, 1938, because of the development of a skin eruption among all members of the family.

The story was that a friend had presented them with a kitten of which the entire family became immediately very fond. This kitten appeared to be entirely normal, and no evidence of mange was observed until the dermatologic examination of the family disclosed evidence suggesting the desirability of a more careful inspection, which inspection of the kitten's fur then revealed a severe patchy type of mange.

The mother presented angry, circinate patches involving the right hand, the right wrist and the right ear. These patches showed raised, apparently peripherally extending erythematous borders with evidences of a tendency toward central clearing and profuse scaling. There was crusting in some areas. The younger son presented identical circinate patches, with raised erythematous borders, central clearing and central scaling. These were located on the right side of the chest and right side of the neck. In the vertex of the scalp there was a rounded area made up of partial alopecia, many short broken-off hairs, and profuse generalized scaling involving the entire scalp. The older son developed ringworm infection of the scalp only. There were two rounded patches possessing morphologic characteristics identical with those described for the brother. The father had vaguely outlined patches of erythema and scaling on the left cheek—clinically more closely resembling seborrheic dermatitis than tinea.

Thorough mycologic studies were done only in the case of the younger

son Scales removed from a circinate lesion on the chest were found to contain *Microsporon lanosum*. The history and clinical findings were such as to justify the logical conclusion that this same fungus was the cause of the typical *tinea capitis* present in both boys and the typical *tinea circinata* affecting the mother. It was not considered that the nondescript patches of erythema and scaling involving the father's cheeks could be safely interpreted as a *Microsporon* infection.

In treatment, the mother showed striking improvement in one week after alternate applications of tr metapben and an ointment containing phenol, ammoniated mercury and salicylic acid. Her angry circinate lesions were reduced to vague macular remnants in this one week of treatment. During the subsequent ten days, the small residual lesions remained stationary and a change in fungicidal therapy was made. An alcoholic solution containing 3 per cent salicylic acid, 6 per cent benzoic acid and 3 per cent iodine was prescribed for use twice daily, to be followed in twenty minutes by the application of a 20 per cent sodium thiosulfate lotion. A 6 per cent sulfur and salicylic acid ointment was applied each evening. On this program of repeated fungicidal applications, complete clearing of all residual traces was accomplished in five weeks and the skin remained entirely clear during a subsequent six months' period of observation.

In the treatment of the younger son, all lesions on the neck and chest disappeared completely following one week of applications of tr metapben alternating with an ointment containing phenol, ammoniated mercury and salicylic acid. In treatment of his scalp, all the hair was shaved off quite closely and the same local applications were used. The scalp, however, showed no response to the remedies found to be spectacularly successful on the neck and chest. A special program of care was then outlined for the scalp, and this included applications of an alcoholic lotion containing 3 per cent salicylic acid, 6 per cent benzoic acid and 3 per cent iodine, to be followed twenty minutes later by a 20 per cent aqueous solution of sodium thiosulfate. Each evening a 6 per cent sulfur and salicylic acid ointment was applied. This intensive program was followed by apparently complete clearing of the scalp in about twelve days, with slight recurrences later. Continuation of the procedure of keeping the scalp shaved closely and the continued use of fungicidal applications led to more gradual disappearance of small residual traces in the course of approximately two months. A final check-up examination eight months following the onset of infection revealed no trace of the infection.

The older boy recovered from his *tinea capitis* infection in about ten weeks of treatment along lines identical with those described for his brother. Eight months following the date of infection, careful inspection of his scalp revealed no evidence of recurrence.

The father applied to his affected cheek each evening an ointment containing 6 per cent sulfur and 6 per cent salicylic acid and the cheek cleared completely in about five weeks. Almost complete recovery was apparent in about ten days.

It is well recognized that ringworm of the scalp develops rarely after the age of puberty. This fact explains the marked scalp involvement in the two children of this family and the freedom from scalp infection exhibited by the mother and father.

The following pertains to an unusual case of severe *Microsporon* infection of the feet. This organism is a frequent cause of ringworm of the scalp but is not recognized as a common cause of fungous infection of the feet.

**Case III.**—W G, a man of forty-six, had suffered most of his life from a severe fungous infection of the feet. He sought the advice of many physicians, including eminent specialists, but no one was successful in helping him. There was no discomfort at all, but he was determined to eliminate the complaint if possible and sought dermatologic advice again. He felt sure that there was no real cure for his trouble, but he wanted to take the chance that, under guidance, he might stumble upon something that would either help him or cure him. He cooperated faithfully for many months.

Examination in June, 1938, revealed evidences of one of the severest and most deep-seated macerating types of fungous infection conceivable. The interdigital spaces were loaded with a heavy, whitish, macerated material extending very deeply, as determined by curettage. The toenails showed evidences of undermining and opacities, and there was an extreme scaling reaction extending over the balls, soles, and heels of his feet.

This case of dermatophytosis was completely asymptomatic. There were no sensations of itching or burning. This point is worth stressing because of the common misconception that all fungous infections must itch.

The mycological studies in this case were exceedingly interesting. Material from between the toes and scales from the heels showed plentiful mycelial threads, and cultural studies brought identification of the organism as *Microsporon lanosum*. This fungus is a common cause of ringworm of the scalp and adjacent areas, but has not been reported as a common cause of fungous infections of the feet.

An intensive program of treatment, consisting of liver extract by mouth, copper sulfate soaks, and x-ray, brought about 95 per cent clearing in four months. A total of 450 R units of x-rays were employed.

This gratifying degree of improvement was maintained for four months, to the complete satisfaction of the patient. At this point, the patient went away on two successive sking trips and wore heavy woolen socks on each occasion. The combination of violent exercise and the wearing of woolen socks seemed to precipitate a decided relapse and the condition returned to its original appearance.

Intensive treatment was resumed and the original program of treatment was enlarged upon, but no further x-ray treatment was employed. A number of fungicidal agents were used, and these included copper sulfate, salicylic acid, ammoniated mercury, *pix pin*i, red mercuric sulfide and formalin. In addition, the patient received ultraviolet light, intracutaneous injections of autogenous fungous extract, crude coal tar, and vitamins A, B<sub>1</sub>, B<sub>2</sub>, C and D in large doses.

During this second course of intensive therapy, only slight improvement took place in the course of three months.

**Case IV.**—F G., a man of about sixty years of age, sought advice in May, 1937, in regard to some patches on various aspects of his legs. These were circinate and were made up essentially of erythema and scaling. There



were evidences of central clearing and of a peripheral spread. The morphology was strongly suggestive of *linea arcuata*.

The third and fourth interdigital spaces of both feet presented evidences of a severe, deep-seated macerating type of dermatophytosis. The toes were closely jammed together and, evidently, the spaces between were kept shut tightly at all times, thus creating a condition of warmth and moisture favoring a fungous type of infection. This infection of the toes was stated to have been present for fifty years.

Abundant scales were removed from the arcuate patches on the patient's legs and these showed on direct microscopic examination a few isolated spores. Cultural studies disclosed a definite yeast type of organism.

In treatment, an alcoholic lotion containing 3 per cent salicylic acid, 6 per cent benzoic acid and 3 per cent iodine was applied daily for a week and every two days for eight days, with no improvement of the legs but with slight improvement of the feet. This therapeutic approach was then changed. A combination of 6 per cent sulfur and 6 per cent salicylic acid in a vaseline base, used in conjunction with three x-ray treatments totaling 175 R units, then brought about complete clearing of the legs in the short interval of ten days.

The legs remained clear for six months but, during the following December, there was recurrence of a solitary papulosquamous lesion on the anterior surface of the left leg. This plaque was raised and deeply erythematous and showed layered silvery scales suggestive of psoriasis. This plaque cleared slowly but completely in one month after four more x-ray treatments and the resumption of the use of sulfur and salicylic acid ointment.

The interdigital spaces of the feet improved only moderately following the use of fungicidal remedies but, on a trip to Florida, the patient bathed frequently in a body of water having a strong sulfurous odor and the feet cleared almost completely in the course of about two weeks.

**Case V**—H R., a man of forty-four years, was first examined in April, 1939, and presented evidences of a severe interdigital scaling and macerating type of fungous infection of the feet. Mycological studies revealed abundant mycelial threads upon direct microscopic examination, but cultural studies were unsuccessful and it was not possible to make species identification.

The interdigital scaling and maceration showed prompt diminution following the application of an alcoholic lotion containing 3 per cent salicylic acid, 6 per cent benzoic acid and 3 per cent iodine. This solution was applied every two days at the start and every four days later. After a month of treatment, a gratifying result was obtained and only trivial remnants were apparent.

The following cases (Nos VI, VII, VIII, IX, X) all represent clinical studies of the *Monilia* type of infection. Illustrations are given in regard to involvement of such regions as the fingernails and toenails, interdigital spaces of the feet, the palms and soles, etc.

**Case VI**—D S., a man of fifty-one years, was under observation for twenty-one months from November, 1936, to August, 1938. The presenting



actions to 0.1 and 0.2 c.c injections of this material increased from a negative reaction to a violent vesicular reaction on the fifth inoculation. A total of twelve such injections were given. During this procedure, the feet cleared once again quite completely except for mild maceration in the fourth interdigital space only. This spectacularly improved state persisted during the eight succeeding months of observation.

In June, 1939, eighteen months following the final period of treatment, the patient telephoned to report that during this long interval his feet had remained perfectly comfortable and completely clear. He stated that he had observed a mild flare-up while vacationing in Bermuda, but that this had quieted down promptly after several applications of one of the preparations previously advised. This was the alcoholic solution containing 3 per cent iodine, 3 per cent salicylic acid and 6 per cent benzoic acid.

A highly satisfactory end result was obtained in this case and this result was attributable to three chief influences: (1) a summer spent barefoot on his boat, (2) intracutaneous injections of an autogenous *Monilia* extract, and (3) crude coal tar ointment. The response to these measures was striking. They were not used simultaneously but in separate stages of the treatment scheme.

The following is presented as a proved case of mycosis fungoides associated with heavy infection of the skin with *Monilia albicans*.

**Case VII—C**, a man of sixty years, gave a lengthy story of having suffered for six years from the severe manifestations of mycosis fungoides, proved by biopsy studies and checked by several outstanding pathologists.

The picture was essentially that of severe generalized erythema and scaling. The face was scarlet in color and showed profuse scaling. The ears were edematous and showed a peculiar cyanosis. The eyebrows and eyelid margins presented marked scaling, and the scalp showed what seemed to be a severe squamous type of seborrheic dermatitis. The hands were involved, with extreme changes of a keratotic nature. The palms were thickened and horny and somewhat verrucous in some areas. There were deep painful fissures. The feet showed severe scaling and maceration of the interdigital spaces and extreme scaling of the soles. The heels were encased in a cast made up of verrucous and keratotic material.

Previous treatment by means of x-rays had brought temporary improvement of a symptomatic nature with lessening of the itching. Large doses of vitamin D and generous exposure to natural sunshine brought about almost complete relief of discomfort.

The mycological studies were extraordinarily interesting. All specimens removed from the heels, palms, and interdigital spaces of feet were loaded with mycelia and in all three of these areas positive cultures of *Monilia albicans* were obtained. Mycological studies of material removed from the trunk, left leg, ears and scalp were all entirely negative.

In treatment, a 20 per cent salicylic acid ointment was remarkably successful in removing the horny encasement of the feet. Large doses of liver

extract and haliver oil with viosterol seemed to improve the general condition somewhat. Intracutaneous injections of an autogenous fungous extract were apparently ineffective. Except for the feet, the total gains from therapy were rather small.

The next case, illustrating a yeast infection, was studied carefully from the viewpoint of the probable relation to various sources of chemical irritation.

**Case VIII.**—E. W., a nurse forty years of age who was actively engaged in assisting several doctors in a busy office practice, began to notice a disturbance affecting, first, the right hand and, later, the left. After a year of intermittent difficulty she sought advice. There was a definite history that the hands would clear up completely within a week while she was on vacation and would remain so until she returned to work. This story was strongly suggestive of a type of contact dermatitis related to the chemicals employed in her work. It was stated that both lanolin and boric ointment seemed to have very unpleasant irritating and drying effects, and this also suggested an unusual type of skin reaction to external contacts.

Examination disclosed a moderate amount of erythema, and scaling and fissuring involving the flexor surface of several fingers. These changes were not entirely specific in morphology. The index fingernail of the right hand showed a considerable amount of undermining, with an accumulation of a cheesy type of material. The nail was thickened and showed a peculiar whitened effect. This fingernail alteration was strongly suggestive of a fungous infection. The preliminary clinical diagnosis was fungous infection combined with contact dermatitis, two conditions which are commonly associated.

Patch tests carried out in an attempt to identify the nature of the contact allergen were negative. The history suggested a possible sensitization reaction to either soap, bon am, or rubber gloves. The standard forty-eight-hour patch tests with these substances were all entirely negative.

The involved fingernail was so badly diseased as to permit complete removal without pain. Mycological studies revealed the presence of a yeast infection of the *Monilia* species. The diagnosis of yeast infection was thus established, but it was considered that there was a definite factor of occupational nature, operating along lines of chemical irritation apart from true allergy. The patch tests tended to exclude the existence of true contact allergens.

Treatment was carried out by means of a program consisting of haliver oil and liver extract by mouth and 2 per cent ammoniated mercury ointment locally. A very successful result was obtained. All areas except the fingernail cleared promptly.

**Case IX.**—E. J., a woman of thirty-three years, appeared in January, 1939, complaining of a disturbance of the index finger and thumb of the right hand. Examination disclosed a marked degree of erythema and edema, with a moderate amount of scaling involving the nail beds of the right thumb and index fingernail.

Mycological studies revealed evidences of a yeast type of infection of the *Monilia* species

In treatment, a 3 per cent alcoholic solution of iodine was applied twice daily, this was allowed to dry and was followed by the application of an ointment containing 6 per cent salicylic acid and 6 per cent sulfur. Abbott's ABDG capsules were prescribed in a dosage of four daily and 550 R units of x-rays were administered in divided doses. Complete clearing took place in six weeks.

Case X—E J., a woman of thirty-five years, was examined in December, 1937, with a complaint referred to the index fingernail of the left hand. This nail showed extreme deformities and had fallen off several times. All the toenails were involved. The condition had been present for many years. The patient's mother had the same trouble.

Examination disclosed marked changes in the left index fingernail. There were pronounced evidences of thickening, deformities, undermining, grayish discoloration, and whitening effects. All toenails showed these same changes. The appearance was strongly suggestive of both a fungous infection and psoriasis, but there was no concomitant evidence of the latter. There were no skin changes involving the elbows or knees and the skin in general was normal in all respects except for the nails.

Mycological studies, carried out on nail tissue from the left index finger, revealed plentiful branching mycelial threads and cultural studies disclosed *Monilia albicans*. The diagnosis of onychomycosis due to *Monilia albicans* was thus established.

The patient's sole interest was cure of the fingernail. This nail received intensive therapy, and in nine months an apparent cure was established which has persisted for eight months, and with every likelihood that the result will be permanent. More casual treatment of the toenails was relatively ineffective.

Treatment consisted of haliver oil and liver extract by mouth, frequent and thorough removal of diseased nail tissue, fungicidal applications, occasional touching up with bichloroacetic acid, and x-ray therapy. Salicylic acid, benzoic acid, iodine, sulfur, ammoniated mercury, silver nitrate and crude coal tar were employed at various stages.

By persistent use of this program of care, an apparently permanent cure was obtained. At the last visit in May, 1939, the fingernail had been completely normal for eight months. The cure required nine months.

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### EXAMINATION OF THE HEART IN GENERAL PRACTICE

It was approximately a generation ago that the introduction of the x-ray and the electrocardiograph into clinical medicine brought a refinement and a precision to cardiac diagnosis which had hitherto been lacking. But ever since that time the exploitation of these accessory methods has so dominated the cardiologic literature that one might easily gain the impression that the art of physical examination was losing ground before the march of science. Nothing could be further from the truth.

As a matter of fact the technique of physical examination of the heart has been vastly improved by what has been learned from these new methods. The electrocardiograph has furnished us with an understanding of the nature of abnormal rhythms which enables us to recognize most of them now with a stethoscope. The x-ray has provided a check on the accuracy of heart measurements obtained by palpation or percussion which has undoubtedly enhanced their validity. Laboratory procedures are often helpful and sometimes necessary but, in cardiology, they are of secondary importance as compared to the history and the physical examination.

The history of the cardiac patient is a particularly important part of the examination because, in certain cases, such as for instance angina pectoris or paroxysmal tachycardia, it may furnish the only evidence of the nature of the disorder.

#### FAMILY HISTORY

In inquiring into the state of health or causes of death of antecedents and siblings, the examiner has in mind that three of the commonest types of heart disease show a definite hered-

itary predisposition, namely coronary disease, hypertension and rheumatic heart disease

### PAST HISTORY

In reviewing the life history of the individual, one tries to do two things (1) to uncover any etiologic factors of heart disease, such as rheumatic fever, chorea, syphilis, hypertension, or hyperthyroidism, and (2) to expose any evidence of heart disease antedating the present illness. Approximately one-half of adult patients with rheumatic heart disease give no history of prior rheumatic fever, and a smaller but important percentage of patients with cardiovascular syphilis disclaim any knowledge of primary or secondary lesions. Negative histories in regard to these infections are therefore of limited value. Since the most important predisposing causes of coronary disease of which we are aware are hypertension and diabetes, inquiry should be made into the existence of these conditions prior to the present illness.

In reviewing the patient's past history one also likes to obtain an idea of the functional capacity of the heart before the patient was aware of anything being wrong with it. During childhood was he able to carry on the usual games with his playmates? In youth did he lead a strenuous, athletic life or a sedentary one? Has he kept up regular physical exercise in adult life? The answers to these questions will furnish an idea as to the underlying functional capacity of the heart by which the degree of subsequent impairment may be judged. In a woman with children the appearance of cardiac symptoms during the strain of pregnancy should be inquired into. The results of previous examinations, especially in regard to murmurs and blood pressure, may throw light on the existing situation.

### PRESENT ILLNESS

It is well to let the patient tell the story of his complaint as far as possible in his own words. He will be anxious to unburden himself of it and his own spontaneous description of symptoms may be more vivid and meaningful than his replies to cross-examination. The examiner should attempt to fill the gaps in the patient's story by appropriate questions. The common symptoms of cardiac failure are reviewed one by

one, and an appraisal is made of their validity and their relation to effort, etc

**Dyspnea**—With dyspnea, for example, inquiry is made first into whether it is related to effort or not and, if it proves to be the dyspnea of effort, just how much exertion it takes to bring it on. Does it take three flights of stairs or merely walking on the level? In this way a rough quantitative idea of the functional capacity of the heart may be gained which is superior to any other functional tests which are available

If the dyspnea is not related to exertion, it may be one of two types. The first is the sighing respiration type. These individuals complain that while at rest they often have a feeling that they are not getting enough air and they have an impelling desire to take a deep breath. Such patients will often be observed to sigh during the interview. This is a symptom which is associated with nervous fatigue and is not related to organic heart disease. The second type of dyspnea at rest is paroxysmal nocturnal dyspnea. These patients are awakened from sleep by intense dyspnea which causes them to sit up in bed gasping for breath or to rush to the window for air. It is a serious symptom and is brought about by relative left ventricular insufficiency with congestion of the pulmonary circuit. It is seen in syphilitic aortic regurgitation, hypertension, and occasionally following infarction of the left ventricle. Curiously enough some of these patients are able to carry on heavy manual labor during the day without dyspnea of effort.

**Orthopnea**.—Most patients with severe dyspnea of effort have more or less orthopnea. As the degree of orthopnea furnishes additional evidence of cardiac functional capacity, one attempts to quantitate this by ascertaining the number of pillows required at night.

**Cough**.—This is a relatively late sign of pulmonary congestion. It is usually dry or productive only of white frothy sputum. Exceptions to this are the abundant pink frothy sputum seen in acute pulmonary edema and the gross hemoptysis in mitral stenosis. Cough may also result from direct pressure on the recurrent laryngeal nerve of an aneurysm or a dilated left auricle.

**Palpitation**.—Palpitation or awareness of the heart's beat always merits further descriptive analysis. The key questions to be answered are: Is it forceful? Is it regular? Is it rapid,



and if so, how rapid? Is it related to exertion or to rest? Does it start abruptly and end abruptly?

Let us consider the various types of palpitation in light of their subjective manifestations. The type of palpitation which all of us experience on violent physical exertion is, of course, felt to a greater degree or on less effort in people who are in poor physical condition as well as in patients with heart disease or neurocirculatory asthenia. It is so often seen in nervous patients that its value in the diagnosis of heart disease is limited.

One of the most common types of palpitation of which patients complain is that produced by extrasystoles. Many patients have extrasystoles of which they are unaware, but when they do notice them, they can usually give a recognizable description of them. This is of some importance because they may not be present during the examination. Extrasystoles are much more apt to occur at rest and frequently the patient notices them only while he is in bed. They may manifest themselves in various ways. As a rule only the forceful beat which comes after the extrasystole is felt. The long diastolic pause allows the ventricle to overfill and it responds with a contraction of increased vigor. Patients often describe this as a feeling as if the "heart flopped over in the chest." In nervous patients and in patients with aortic regurgitation, the extrasystoles may be associated with sharp stabs of pain which are quite disturbing. Other patients are aware of the pause and are concerned by it.

Paroxysmal tachycardia is often recognizable from the patient's description of it. The characteristic features are the sudden onset and offset of *very* rapid heart action which the patient frequently describes as a "fluttering" sensation in the chest. It is associated with a feeling of weakness and giddiness on exertion. It is usually not related to exertion and lasts from a few seconds to hours or days. In patients with heart disease it may give rise to heart pain.

Auricular fibrillation may give rise to a form of palpitation which the patient describes as "tumultuous" heart action. He is impressed by its irregularity. "It seems to skip and jump all over the place." Many patients with auricular fibrillation do not have palpitation at rest, but most have it on exertion.

**Pain.**—If the patient complains of heart pain, it is necessary to get an accurate description of it in order to evaluate its significance. The occurrence of stabs of precordial pain with extrasystoles has already been mentioned. In neurocirculatory asthenia there may be precordial pain on exertion. In this condition it is apt to be sharp in character and associated with palpitation and dyspnea. In certain types of heart disease, particularly in individuals with hypertension or mitral stenosis who are leading active lives, an aching precordial discomfort appears at the end of the day and is relieved after some hours of rest. The constant boring upper mid-chest pain sometimes associated with syphilitic aortitis is familiar.

The term "angina pectoris" should be reserved for a type of chest pain which has certain peculiar characteristics. It is not necessary to dwell upon the various distinguishing features of angina pectoris here. In brief it is characteristically a paroxysmal substernal or precordial pain which is brought on by exertion, excitement, eating, or exposure to cold, which lasts from a few seconds to a few minutes (never more than half an hour), and which is relieved by rest or nitroglycerine. It may radiate down the inner aspect of the left arm or both arms and sometimes is present only in the arms without any chest pain.

The peculiar feature of the pain of angina pectoris is that it almost always has in it an element of constriction. Typical complaints are "It is like being squeezed in a vise," "It is like a steel wire pulled tight around my chest," "It is as if a cannon ball were resting on my chest," "It cuts my wind off," "It strangles me." The literal meaning of angina is "strangling" or "suffocation," and this is the feature which most clearly distinguishes it from other types of heart pain.

The pain of coronary thrombosis differs from that of angina pectoris in being more severe and of longer duration. Any attack of angina which lasts more than half an hour suggests coronary thrombosis.

**Edema.**—A history of swelling of the ankles is of some interest if extracardiac factors, such as thrombophlebitis, varicose veins, etc., can be ruled out.

It is important for the examiner to know what drugs the patient has been taking, in what doses and what the effect has

been In regard to digitalis, this knowledge is almost essential before treatment can be started

### PHYSICAL EXAMINATION

A proper examination of the heart necessarily involves a complete physical examination One keeps an eye out particularly for factors of possible etiologic importance, such as arteriosclerosis, syphilis, infection, hyperthyroidism, nephritis, and anemia However, only that part which has to do directly with the heart can be touched upon here In some cases the most important evidence of the nature of the disorder will be found outside of the heart, *e g*, the retinal exudate in malignant hypertension or the blood pressures in arms and legs in coarctation of the aorta

**Inspection**—It is preferable to have the examination in bed or on an examining table so that observations may be made in both the upright and recumbent positions The general appearance of the patient is, of course, important One notes his position of choice in bed and the presence or absence of anxiety or respiratory distress Pallor may be caused by any of several factors, besides anemia and active infection one finds it especially in association with aortic regurgitation Cyanosis is, of course, a common feature of cardiac failure, particularly when there is pulmonary edema In the absence of failure it is found in certain types of congenital heart disease, marked mitral stenosis and emphysema In certain cases of coronary thrombosis with associated peripheral circulatory collapse there is a mixture of cyanosis and pallor which gives a characteristic slaty-gray color Jaundice in a cardiac suggests severe hepatic engorgement or a recent pulmonary infarct Petechiae are searched for in the skin and mucous membranes—particularly the inner surfaces of the eyelids and cheeks

Coming to the examination of the thorax, one observes its shape and respiratory excursion and the presence or absence of Hoover's sign (inspiratory retraction of the costal margin due to flattening out of the diaphragm—as from emphysema or pleural fluid) In individuals who developed cardiac enlargement in early childhood a precordial bulging of the ribs may be noted

Inspection of the vessels of the neck should then be carried

out. The external jugular veins are not normally filled with blood in the upright position and their distention is one sign of right ventricular failure. Marked pulsation of the jugular veins may easily be distinguished from carotid arterial pulsations by light pressure with the finger which will obliterate the venous pulse. Increased arterial pulsations of the carotids are seen with free aortic regurgitation. Tortuosity and systolic wrinkling of the brachial arteries may be seen with peripheral arteriosclerosis. The entire thorax should be inspected for pulsations. In normal persons with thin chest walls the apex impulse may be clearly visible and, in many, an epigastric pulsation as well. In patients with right ventricular hypertrophy a systolic impulse can often be seen in the third and fourth interspaces, a little to the left of the sternum. At the base a visible systolic impulse is suggestive of aneurysm of the aorta. This is usually seen to the right of the sternum. In many instances an impulse which is visible is not palpable, and the reverse is also true.

Systolic retraction of the lower ribs and interspaces on the left (Broadbent's sign) is suggestive of adhesive pericarditis, but it is also seen with marked cardiac enlargement from any cause.

**Palpation**—Simultaneously with the inspection of the thorax the radial arteries may be palpated and note made of the rate, rhythm, quality of arterial wall, tension, shape of the pulse curve (*e g*, Corrigan or plateau type, etc.), and equality of the two pulses. The presence of *pulsus alternans* may sometimes be detected by palpation of the radial pulse, although it is much more easily demonstrated with the sphygmomanometer. It consists of alternate weak and strong pulse waves *evenly spaced* and is a serious prognostic sign.

The apex impulse of the heart can be palpated in most normal people and in a still greater proportion of persons with cardiac enlargement. It furnishes the most accurate and simple method of localizing the left border of the heart, the point taken being that of the *maximum* apex impulse, not the outermost palpable impulse. This is normally found in the fifth intercostal space within the midclavicular line. An apex impulse which is maximal 1 cm or more outside of the midclavicular line is evidence of enlargement (or displacement) of the heart to the left.

The character of the impulse is of some importance In the nervous or hyperthyroid individual one recognizes the overactive heart which pounds against and shakes the chest wall In fully developed mitral stenosis, the impulse is a quick localized tap—the French call it "*choc en dôme*" With the big left ventricle of aortic regurgitation, on the other hand, one notes a heaving, sustained thrust In bundle-branch block, a reduplicated apex impulse can often be observed

With well-marked mitral regurgitation or stenosis, one may feel at the apex a systolic or diastolic thrill as the case may be Thrills are best felt with the patient holding his breath in expiration The true thrill must be of a definitely sustained, purring character It is essentially a murmur which is coarse enough to be palpable, and it should not be confused with the brief vibrations set up by the impact of an overactive heart against the chest wall As the palpating hand goes up to the base one may feel the diastolic closure of the pulmonic valve in the second left interspace This finding is usually associated with mitral stenosis and corresponds to marked accentuation of the pulmonic second sound The diastolic closure is seldom felt to the right of the sternum, but occasionally in this area one detects the gentle heave of an aneurysm Systolic thrills over the pulmonic or aortic valve areas are evidence of stenosis of the underlying orifice Thrills in the arteries of the neck are difficult to interpret They are not uncommon in free aortic regurgitation without stenosis In some cases of marked aortic regurgitation one may also feel a diastolic thrill along the left sternal border

**Percussion**—This is probably the least accurate method of cardiac mensuration, but with practice and with a full realization of its limitations, it may be employed with profit Its accuracy is greatest in delineating the extreme left border of the heart, which lies close to the chest wall, and its accuracy is least in outlining the descending arch of the aorta to the left of the sternum

Immediate, or one finger, percussion is often more satisfactory than the usual method A useful trick, if in doubt, is to place the stethoscope anywhere on the chest while percussing and one will find the change in percussion note at the border brought out more distinctly However, in the obese

and the emphysematous, percussion may be quite unsatisfactory

Percussion is of special value in pericardial effusion. Here the apex impulse is usually not palpable, but the contrast between the lung resonance and the pericardial flatness is sharp. One may also note a change in the percussion outline of the heart with change of position. In the upright position, the weight of the fluid in the pericardial sac causes it to mushroom out at the bottom giving a so-called "water bottle" outline. In the recumbent position, some of the fluid gravitates toward the head, with the result that the lateral borders become more nearly parallel.

**Auscultation.**—There are normally two and sometimes three heart sounds. The *first heart sound* is rather soft in quality and corresponds in time to the onset of ventricular systole and the closure of the mitral and tricuspid valves. The valve closures are the most important element in the production of the first sound, it being doubtful whether the muscular contraction contributes any sound at all. The quality of the first sound may be altered by various factors, notable among them being mitral stenosis, prolonged auriculoventricular conduction and bundle-branch block. In well-marked mitral stenosis one may hear an accentuated and abrupt first sound at the apex with no systolic murmur whatever. Slight prolongation of auriculoventricular conduction beyond 0.20 sec causes a diminution in the intensity of the first sound while a further delay in conduction may bring about a presystolic gallop rhythm. Reduplication of the first sound may be caused by bundle-branch block with asynchronous contraction of the two ventricles. Slight reduplication of the first sound is occasionally heard in normal children.

The *second heart sound* is caused by the closure of the aortic and pulmonic valves. These valves do not always close synchronously, so that reduplication of the second sound is found not infrequently in normal people, particularly children. In some individuals the reduplication is heard only in one phase of respiration. The pulmonic second sound is normally louder than the aortic second sound in childhood and, as adult life is reached, the aortic second sound becomes relatively louder. Accentuation of one or the other second sound must be marked to be significant. The pulmonic second sound is

accentuated in conditions which give rise to increased pressure in the pulmonary circuit. These are mitral stenosis, left ventricular failure and patent ductus arteriosus. The aortic second sound is accentuated in hypertension and in syphilitic aortitis. Either the first or second sounds may, of course, be obliterated by murmurs, and both are muffled by emphysema or pericardial effusion.

The *third heart sound* occurs simultaneously with the opening of the mitral and tricuspid valves. It is separated from the second sound by a long enough interval so that it cannot be mistaken for a reduplicated second sound. It sounds more like a faint echo of the second sound. The third heart sound is audible in most normal children and many young adults, but it disappears as a normal phenomenon during the fourth decade. In middle age or after it is a distinctly abnormal sign, occurring with dilatation of the left ventricle, and is referred to as a "protodiastolic gallop rhythm." It is observed in failing hypertensive hearts, in infarction of the left ventricle and in myocarditis from any cause. The mechanism of this sound, which is entirely normal in childhood and yet of serious significance in old age, is not clearly understood.

Thanks to lessons taught by the electrocardiograph one is now able to recognize most of the *arrhythmias* with a stethoscope. The normal pacemaker of the heart, the sino-auricular node, may under certain circumstances establish a rate as high as 180 or as low as 40 beats per minute. Sinus tachycardia occurs under a wide variety of conditions which have in common increased sympathetic activity. It is not affected by carotid sinus stimulation except to exhibit slight, temporary slowing in some cases. Sinus bradycardia is commonly observed in young athletic males convalescent from acute infections or operations. In extreme cases the basal rate approximates that seen in complete heart block, from which it may be readily differentiated by the fact that there is usually sinus arrhythmia present and the rate rises promptly with exercise, whereas with complete block, the rhythm is absolutely regular and unaffected by exercise.

Respiratory sinus arrhythmia is aggravated by deep breathing and diminished by exercise.

*Premature beats* or *extrasystoles* are usually readily recognizable if the basal rhythm is regular. They are characterized

by periodic interruptions of the regular rhythm by an early beat followed by a prolonged diastolic pause. The premature beat may not force out enough blood to produce a palpable radial impulse—resulting in a “dropped beat at the wrist.” It is important to distinguish sharply between these apparent dropped beats, which have no clinical significance, and true dropped beats due to organic heart block. The stethoscope will readily differentiate between the two.

Another test is to have the patient exercise, which will usually abolish the irregularity if due to extrasystoles and aggravate it if due to dropped beats. Since extrasystoles may only occur with a slow heart rate under conditions of complete rest, they may be difficult to elicit during an examination. Having the patient breathe deeply while completely relaxed in the recumbent position will sometimes bring them out. In others, they will appear as the heart slows down after exercise.

No attempt has been made here to distinguish between auricular and ventricular extrasystoles—a distinction which can seldom be made with assurance on physical examination and which is not ordinarily of much importance. Ventricular extrasystoles are approximately ten times as common as auricular. When ventricular extrasystoles occur in the presence of auricular fibrillation they can be recognized on auscultation only when they occur with such frequency as to produce bigeminal rhythm.

When a series of extrasystoles occur in succession it is called *paroxysmal tachycardia*. Paroxysms of ectopic tachycardia may have a duration of seconds up to weeks. The common type of paroxysmal tachycardia is auricular in origin and is characterized by the sudden onset of a regular heart rate of 160 to 220 per minute. Carotid sinus stimulation or pressure on the eyeballs will either restore normal rhythm completely or will have no effect—there is no partial or temporary slowing, it is all or none. For proper manipulation of the carotid sinus the patient should be in the upright position with the head rotated away from the side to be stimulated. The sinus is palpated between the angle of the mandible and the upper end of the sternomastoid muscle. It is pressed firmly against the spine with a massaging motion. The right carotid sinus is usually more sensitive than the left, but if stimulation of one is not effective, the other should be tried.



Paroxysmal ventricular tachycardia is far less common than the auricular variety and is usually a complication of serious myocardial injury such as infarction. It may some times be recognized by the fact that the heart sounds vary slightly both in intensity and rate. It is not affected by carotid sinus or eyeball pressure.

*Auricular flutter* is usually associated with a rapid regular ventricular rhythm, but the rate is not as rapid as in paroxysmal tachycardia and may change abruptly from time to time. Carotid sinus pressure often produces temporary slowing but does not abolish the tachycardia. In some cases the ventricular response is so irregular that it is impossible to distinguish it from auricular fibrillation, to which it is intimately related.

*Auricular fibrillation* is characterized by total irregularity in rhythm and force of the heart beat. The irregularity is not abolished by exercise or by any other maneuver. Auricular flutter and fibrillation are presumptive evidence of heart disease. Since they are particularly apt to occur in hyperthyroidism, the basal metabolic rate should be determined in all cases not readily explained on the basis of mitral stenosis or coronary disease.

*Systolic murmurs* are not always easy to appraise. Much depends on the presence of other signs, such as cardiac enlargement or a diastolic murmur and on the location and intensity of the murmur. Functional systolic murmurs are usually soft and blowing in quality and are most commonly located in the pulmonic area. In a smaller percentage of cases the murmur is heard best lower down in the fourth intercostal space to the left of the sternum. It is seldom maximal at the apex. Such murmurs are heard in about 40 per cent of normal children and in many healthy adults, especially in pregnant women. Strenuous exercise brings out this murmur with great frequency in normal individuals. It is heard at its best in hyperthyroidism, where it may be very loud and even associated with a friction rub in the pulmonic area. Such murmurs are also common in febrile states and in anemias and may persist for months after the patient has regained normal health.

Systolic murmurs which are loud or which are maximal at the apex usually mean organic disease of some sort. Apical systolic murmurs are caused by stretching of the mitral ring from left ventricular dilatation (in hypertension, aortic regur-

gitation, coronary disease) and from actual deformity of the valve (organic mitral regurgitation) Systolic murmurs in the aortic area are heard in dilatation of the ascending aorta from hypertension, syphilis, or arteriosclerosis and in aortic stenosis Because of the frequency of functional murmurs in the pulmonary area one is particularly skeptical of systolic murmurs in this region—the more so perhaps because the only organic murmurs maximal in this area are of congenital origin, either pulmonary stenosis or patent ductus arteriosus In the latter condition the murmur may be entirely systolic in time, but it is more commonly continuous throughout the heart cycle with systolic accentuation A peculiar type of systolic murmur is the so-called Roger murmur which is heard in patency of the intraventricular septum It is very loud and yet strikingly localized to the fourth left intercostal space next to the sternum

*Diastolic murmurs* are often harder to hear than systolic murmurs, but they are much more important The two most common diastolic murmurs are the aortic and the mitral, the contrasting features of which are listed in Table 1 The dis-

TABLE 1

## CONTRASTS BETWEEN AORTIC AND MITRAL DIASTOLIC MURMURS

	<i>Aortic</i>	<i>Mitral</i>
<i>Time</i>	Early diastole.	Mid or late diastole.
<i>Pitch</i>	High, blowing	Very low, rumbling
<i>Position</i>	Aortic area and along left sternal border	Near apex
<i>Transmission</i>	Often widely transmitted	Localized
<i>Optimum Position for Hearing</i>	Upright or leaning forward	Left lateral position
<i>Stethoscope</i>	Bowles type	Bell type

tinguishing features of the two are so well-marked that there should never be any difficulty in differentiating them The faintest aortic diastolic murmurs are of very short duration and their quality approaches that of the breath sounds All such murmurs are more clearly heard when the patient's breath is held in deep expiration This not only abolishes extraneous breath sounds, but brings the heart closer to the chest wall

The chief difficulty in hearing mitral diastolic murmurs is that the pitch is so low that it escapes recognition as a murmur The aortic diastolic murmur trails directly off the second

sound, and may eventually obliterate it, but the mitral diastolic murmur is always separated from the second sound by a distinct interval, corresponding to the interval between the second and third sounds. Indeed, one is frequently confronted with a question as to whether one is dealing with a loud third sound or a mitral diastolic murmur, a question which is decided on the basis of the duration of the sound. When aortic diastolic murmurs develop under observation, they are first heard along the lower left sternal border. Only when they become more well-marked can they be heard in the so-called aortic area to the right of the sternum. When fully developed the murmur is widely transmitted from base to apex. The mitral diastolic murmur, on the other hand, is never transmitted to the base and is often localized to an area 2 cm in diameter. The aortic diastolic murmur is best heard in the upright position or leaning forward using a Bowles type of stethoscope (which screens out low-pitched vibrations). The mitral diastolic murmur is usually best heard in the left lateral position using a bell stethoscope.

Not every diastolic murmur means disease of the corresponding valve leaflets. Dilatation of the aortic ring in hypertension, for instance, may result in functional aortic regurgitation even with a very high diastolic blood pressure. A similar situation in the pulmonic system presumably accounts for the Graham-Steell murmur found in rare cases of advanced mitral stenosis. With left ventricular dilatation one may hear a short mid-diastolic murmur at the apex. This was first described by Austin Flint in aortic regurgitation but has since been observed in hypertension and in acute rheumatic myocarditis without valvular disease.

I have deliberately omitted any reference to tricuspid valvular disease because it is so rarely seen clinically and because the diagnostic difficulties are somewhat out of proportion to its importance.

I have also avoided mentioning the various peripheral signs of aortic regurgitation, such as Duroziez's sign, pistol shot pulse, capillary pulse, etc. Although they still figure largely in the textbooks and courses in physical diagnosis, they add no information not obtainable with a sphygmomanometer. Taking of the blood pressure is, of course, part of every heart examination, but the technique need not concern us here.

The *pericardial friction rub* is characteristically a coarse, scratchy to and fro sound in systole and diastole. It is usually heard near or over the sternum, is often intensified by pressure with the stethoscope, and persists in undiminished intensity when the breath is held. It is apt to be evanescent. Sometimes it is entirely systolic in time and may be confused with a systolic murmur. A pleuropericardial friction rub may closely simulate it, but it is usually more affected by respiration. Pericardial rubs are heard in pericarditis resulting from infection, uremia, myocardial infarction, or hemorrhage into the pericardium.

A word in closing in regard to the indications for electrocardiography. The electrocardiogram has proved to be of limited usefulness in the diagnosis or prognosis of chronic rheumatic valvular disease. In syphilitic heart disease it has some value in affording evidence of myocardial damage. It is of particular value when there is a doubtful clinical diagnosis of cardiac infarction in the remote or recent past, in obese or emphysematous individuals with dyspnea in whom physical examination is unsatisfactory, in unravelling obscure arrhythmias, and, occasionally, in furnishing evidence of active rheumatic myocarditis. It is often negative, however, in the presence of obvious heart disease.



## CLINIC OF DRS J D SPILLANE AND PAUL D WHITE

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#### THE DIFFERENTIAL DIAGNOSIS OF CHEST PAIN

PAIN in the chest may be a manifestation of many widely differing disease processes. As the outstanding complaint, or as a minor accompaniment to more distressing symptoms, it may result from diseases of the heart and great vessels, lungs and pleura, vertebrae, spinal cord and its nerve roots, chest wall, and the upper abdominal viscera. The site of the chest pain is not necessarily its place of production. Thus, in elucidating the cause of chest pain in an individual we must, by careful history taking and physical examination, search for signs of disorder both within the chest cavity and in surrounding structures. That search is frequently a difficult one, especially so for the following reasons.

In the first place, accuracy in describing the locality of pain begins to decline as soon as the pain ceases. This is of the greatest importance.

Secondly, despite much writing to the contrary there is nothing very characteristic about the *nature* of the various types of chest pain that can be experienced. The pain of angina pectoris may vary from a mild ache under the sternum to a tearing, crushing sensation throughout the chest that sends the patient into syncope. Pain very similar to that in the former instance may be experienced by patients with flatulent dyspepsia (or aortic incompetence), and a dissecting aneurysm may faithfully mimic either.

Thirdly, there is always the nervous state of the patient to consider. From the now well-established instances of congenital insensitivity to pain to the more common extreme of cases of acutely reacting sensory systems, we have varying grades of pain susceptibility that determine, to a large extent, the nature of the response and its outward manifestations. It is for such reasons that little can be expected from a study of pain on the

basis of patients' descriptions. Such adjectives as "terrible," "agonizing," "gripping," "vise-like" and "boring" convey little that is exact from one individual to another. Truly, the naming of pains, thus far, is scarcely scientific.

Fourthly, there are instances in which, by "sympathetic" excitation, a diseased heart may give rise to pain in areas remote from the precordium but which are themselves the site of some pathological process. Mackenzie cited the example of reference of anginal pain to a carious tooth, and similar cases have been described such as radiation of pain to the right wrist which had been injured years ago, or to an arthritic spine, or perhaps even to a diseased area in the abdomen or lower back. It may be argued that the threshold for pain in such localities has been lowered by the disease process and that subliminal impulses from the diseased heart may, by summation, lead to the appreciation of pain in those areas. Whether the converse may also occur is less certain. Clinical experience does tend to show, however, that at times a heartache or substernal pain may be excited in the case of a diseased heart secondary to true indigestion, gallbladder colic, or renal calculus.

With these considerations in mind we can proceed to enumerate and discuss the more important causes of pain in the chest.

#### *Cardiovascular Disease and Disorders*

Angina pectoris  
Coronary occlusion  
Pericarditis  
Aneurysm of the aorta  
Aortic incompetence  
Acute cor pulmonale  
Arrhythmia (extrasystoles and paroxysmal tachycardia)  
Nervous tachycardia  
Forceful beating (especially of enlarged heart) in nervous person

#### *Chest (Pulmonary and Pleural) Disease*

Pleurisy and pneumonia  
New growth  
Pulmonary infarction  
Pneumothorax  
Pleural adhesions

#### *Chest (Pulmonary and Pleural) Disease—Cont*

Pleural effusion  
Phthisis  
"Pleurodynia"  
Bronchitis  
Bronchiectasis  
Spontaneous mediastinal emphysema

#### *Esophageal Lesions*

Cardiospasm  
Esophagitis  
Carcinoma

#### *Abdominal Disease and Disorders*

Peptic ulcer  
Gallbladder disease  
Hiatus hernia  
Subphrenic abscess  
Liver abscess

*Thoracic Wall and Spine*

Spinal metastases  
Spondylitis deformans  
Bursitis  
Myalgia  
Mastitis  
Trauma

*Disease of the Nervous System*

Intercostal neuralgia  
Neurofibromatosis  
Herpes zoster  
Pressure on spinal nerve roots  
Spinal cord tumors  
Tabes dorsalis

## DISEASES OF HEART AND GREAT VESSELS

**Coronary artery disease**—Because of its frequency and importance in medical practice we shall first consider this group of cases. Although the precise mechanism of pain production in coronary artery disease has yet to be fully explained, we have copious clinical data at our disposal concerning the attacks of angina pectoris and coronary thrombosis to which such patients are exposed.

A diagnosis of *angina pectoris* is usually made in the case of a middle-aged or elderly person, who may or may not show evidence of arteriosclerosis and hypertension, when he complains on exertion of substernal discomfort, frequently amounting to actual pain, which is relieved by the administration of nitrites. The attacks may be mild and transient or severe and prolonged. They usually occur during or following exertion or excitement, especially after taking a full meal. Some patients, who are more severely affected, however, experience many of their attacks at night or at rest in the day—*angina decubitus*. The severity of the chest pain presents every gradation from mild substernal oppression to intolerable agony. At times, the patient describes his discomfort as being not painful but rather a choking or strangling in the throat or upper chest. *The sensation as a rule starts beneath the sternum, usually in the upper two-thirds, and not over the heart itself.* It may or may not radiate. Spread to the left shoulder and arm is common, but other directions of radiation, such as to the neck and jaw, the right shoulder and arm, and the interscapular region, are not infrequent. An attack of angina pectoris usually lasts but a few minutes, and only rarely over ten minutes in the absence of coronary occlusion or paroxysmal tachycardia.

The relation of such attacks to exercise, their relief by rest and by the administration of nitrites, and the electrocardiographic evidence of coronary artery disease are important points to consider in establishing a diagnosis. While many



cases (about 25 per cent) will show no evidence of heart disease by any method of examination, in others enlargement of the heart, hypertension, gallop rhythm, and murmurs resulting from cardiac dilatation may be encountered. Electrocardiographic changes may be the only evidence of coronary artery disease. Flattening or inversion of the T waves in Leads 1, 2, 3 and 4 are fairly common, while intraventricular and auriculo-ventricular blocks occur less frequently. In addition, transient deviation of the S-T interval and flattening or inversion of the T waves may take place during attacks of angina pectoris.

**Coronary occlusion**—When the lumen of a coronary artery is occluded by a thrombus (or, rarely, by an embolus) one of several things may happen. The patient may drop dead, he may experience sudden severe pain in the chest, perhaps with spread to the neck, shoulders and arms, with symptoms of shock, he may simply experience a sense of oppression beneath the sternum, with dyspnea and a feeling of anxiety, or, lastly, there may be no pain, collapse, or dyspnea and the incident may pass unrecognized.

The pain may be indistinguishable in nature and site from angina pectoris, but its persistence for an hour or more, the associated signs of collapse (*viz* sweating, hypotension, dyspnea, pallor and tachycardia) and the failure of nitrites to afford relief readily suggest the probability of actual occlusion. In addition, coronary occlusion usually results in myocardial infarction which is followed by fever for a few days ( $100^{\circ}$  or  $101^{\circ}$  F), with a moderate leukocytic reaction (12,000–15,000), increased sedimentation rate, and sometimes a pericardial friction rub. Signs of temporary heart failure may follow.

Electrocardiographic changes are of the greatest importance. Within a few hours of the onset there may develop a high origin of the T wave or of the S-T interval from the descending stroke of the R wave in Lead 1 or 3, with a corresponding depression of the S-T interval in the opposite lead, that is, Lead 3 or Lead 1. A distinct Q wave may make its appearance, or it may become exaggerated if already present in Lead 1 when the S-T interval is elevated in Lead 1 and in Lead 3 when the S-T interval is elevated in that lead. Flattening or inversion of the T waves may or may not persist, abnormality of the Q waves tends to be permanent.

In the differentiation of acute coronary occlusion from

acute abdominal crises (such as acute cholecystitis, biliary colic, and perforated peptic ulcer) which may give rise to chest pain, the absence of previous abdominal complaints, a history of previous angina pectoris or other cardiac symptoms or signs, and the presence of hypertension are indications of likely coronary mischief. The site of the chest pain, sternal, or sternal and epigastric, is characteristic of coronary artery disease, whereas acute pain of abdominal origin rarely begins in or involves the chest alone.

Other heart and great vessel conditions that may give rise to chest pain are aortic aneurysm, aortic incompetence, aortic syphilis, pericarditis, and paroxysmal tachycardia. In addition one must keep in mind the condition of *neurocirculatory asthenia*, in which the patient, usually a young adult of nervous disposition, complains of precordial aching, palpitation, and general heart consciousness. Dizziness, faintness, tremor and sighing respiration are other common symptoms which indicate the instability of the nervous state in such patients.

Careful physical examination should enable one to establish the existence or otherwise of the above-named organic heart conditions that may produce chest pain. A history of syphilis and of paroxysmal dyspnea, the presence of murmurs at the heart base, roentgenologic evidence of dilatation of the aorta and the determination of the serum reactions for syphilis will aid the physician in making a diagnosis of *cardiovascular syphilis*. It should be remembered, however, that cardiovascular syphilis may fail to present any of the above symptoms or signs for a long time and that angina pectoris may be its only manifestation.

*Marked aortic regurgitation* with a very low diastolic blood pressure may lead to coronary insufficiency and anginal pains. Angina pectoris may be noted during a paroxysm of tachycardia, but the patient is usually conscious of the disturbance in pulse rate and a careful history should elicit this important fact. The pain of *acute pericarditis* may resemble that of angina pectoris, but its longer duration, the etiologic background (rheumatic or otherwise), the acute nature of the illness and the presence of a friction rub or the later development of effusion into the pericardial sac, should prevent a mistake in diagnosis.

A *dissecting aortic aneurysm* often gives rise to excruciating chest pain of sudden maximal onset, spreading widely to involve the back, lumbar region, and often the legs. Shock may be profound, arterial obliteration may result, most commonly in the legs, but electrocardiographic evidence is usually negative. Chronic hypertension and cardiac enlargement are almost invariably present, roentgen examination is rarely helpful.

*Sudden occlusion of a main branch of the pulmonary artery* may lead to chest pain, first by cardiac dilatation, and second by involvement of the pleura in the ensuing pulmonary infarction. The earlier pain may be slight and readily overlooked, but the pleuritic pain is frequently troublesome and may resemble that of pneumonia. A history of recent surgical operation, the presence of thrombosis in the abdominal, pelvic, or leg veins, the frequency of dyspnea in attacks, signs of shock, and the absence in the electrocardiogram of changes due to coronary arterial occlusion, serve to guide the physician to a correct diagnosis. If the infarction is sufficiently large to embarrass the heart, the right ventricle dilates and we have the condition of *acute cor pulmonale*. In this event the electrocardiogram may be characteristic: an S wave develops in Lead 1, the T wave in Lead 2 tends to be low or inverted, a "Q" wave is found in Lead 3, or is increased in amplitude, and Lead 4 remains normal except for the T wave which may be flattened or inverted. These changes tend to be transient.

#### DISEASES OF LUNGS AND PLEURAE

There are several conditions of the lungs and pleurae which may give rise to chest pain. Such pain may be of sudden onset, occurring in an apparently healthy individual, or it may form a more chronic symptom during the course of an illness such as phthisis or carcinoma of the lungs.

In the former group, *spontaneous pneumothorax*, because of its sudden onset in a healthy person, usually a young adult, presents a striking and an all too frequently overlooked event. The patient most often presents himself to the physician complaining of a pain in some part of the chest, usually the side on which the accident has occurred. The pain is usually of sudden onset, so that the patient can give the exact moment that it occurred and what he was doing at the time, on the other hand the onset may be insidious and attended by little if any

pain The pain tends to be sharp and stabbing, it is usually felt in the midaxillary region but it may be referred to the scapula or beneath the clavicle or may radiate around the chest. Accompanying the pain is a shortness of breath which steadily increases, while the patient is pale, bathed in perspiration and has cold extremities The mental distress is often extreme Cyanosis is rarely marked The physical signs will depend to a large extent on the amount of air in the pleural cavity They are diminished movement of that side of the chest, diminished tactile vocal fremitus, hyperresonance, diminished or absent breath sounds, and in some cases, the coin sound The cardiac apex beat may be displaced towards the normal side The immediate cause of spontaneous pneumothorax is rupture of an air-containing vesicle into the pleural cavity, approximately 80 per cent of all cases of pneumothorax are due to pulmonary tuberculosis, the remaining 20 per cent resulting from pulmonary abscess and gangrene, bronchiectasis, pneumonia, pulmonary infarction, and empyema Among extrapleural causes may be mentioned mediastinal emphysema, subphrenic abscess, perforating ulcer of the stomach or esophagus, and caries of the rib or sternum

Rather less striking in onset may be the pain of *pleurisy*, *pneumonia*, or *pulmonary infarction* The involvement of the pleura in each case produces a sharp, lancinating pain which waxes and wanes with the respiratory movements A short, dry hacking cough is a frequent accompaniment. Sudden cessation suggests accumulation of pleural fluid Diaphragmatic pleurisy causes referred pain along the trapezius ridge when the central portion is affected, and over the lower chest and abdomen when the outer half is affected

Thoracic pain sooner or later attacks a large majority of patients with *pulmonary tuberculosis* and has been attributed to pleurisy, contraction of old cavities, pulmonary congestion, traction on pleural adhesions, and coughing It may be a dull constant ache or pain indistinguishable from that of pleurisy as described above In bronchitis and bronchiectasis pain is rarely a prominent feature, in the former soreness beneath the sternum may attend the bouts of coughing and expectoration, while in the latter condition occasional pleuritic pains may be encountered In a well-established case of bronchiectasis, however, the chronic cough and foul sputum, the transi-

ent exacerbation with fever and chills, and signs of lung involvement with clubbing of the fingers and roentgenologic evidence of dilated bronchi should clinch the diagnosis. To wait for such signs, however, before injecting lipiodol is to deprive many an early case of much benefit. Not all bronchiectatic cavities emit copious foul-smelling sputum.

In a man past middle-life, the sudden appearance, without evident cause, of pain in the chest, dyspnea, or hemoptysis should suggest *cancer of the lung*. Pain is an early symptom in 70 per cent of all cases. It is persistent and often referred to the shoulder, arm, or epigastrium. With it no pleural friction is heard, and, a most important clue, it is not relieved by the accumulation of pleural fluid. Loss of weight, clubbing of the fingers, signs of metastases elsewhere, are all inconstant findings and early diagnosis can only be made by roentgenologic and bronchoscopic studies. The first step in the diagnosis of cancer of the lung is to suspect its presence when any obscure chest condition makes its appearance in an adult past middle-life.

*Acute spontaneous mediastinal emphysema*, through the recent classical paper of Hamman, is now recognized as an occasional cause of sudden substernal distress lasting for hours and simulating coronary thrombosis. The diagnosis may be made by the hearing of a most unusual bubbling or crunching sound at the cardiac apex with every heart beat and may be confirmed by roentgenologic evidence of air in the mediastinum and absence of characteristic electrocardiographic changes.

#### CHEST PAIN OF ESOPHAGEAL OR GASTRO INTESTINAL ORIGIN

Occasionally, confusion and diagnostic errors result from a failure to recall the possibility that pain in the chest may arise from lesions in the esophagus, stomach and duodenum, gallbladder, appendix, liver, or spleen. Although on the whole esophageal lesions are not very common, they may present pretty problems in diagnosis owing to their tendency to mimic painful intrathoracic conditions. Acute inflammation of the esophagus, following ingestion of chemical irritants, and ulcers of the esophagus, may produce burning pain beneath the sternum, aggravated by swallowing.

*Spasm of the esophagus*, usually termed *cardiospasm* when

it occurs at the lower end, may similarly lead to substernal pain which is often accompanied by regurgitation of food or actual vomiting. The intermittent character of the pain, its common localization to a small area behind the sternum, its relation to meals and frequent relief by nitrites may lead the unwary to a diagnosis of angina pectoris. Demonstration of the spasm roentgenologically, following a swallow of barium, confirms the diagnosis. However, organic obstruction from carcinoma and mediastinal tumors may have to be excluded. The shadows of malignancy are usually not slow in making their appearance in such cases.

Periesophageal hernia (*hiatus hernia*) in which a portion of the stomach passes upward through the esophageal hiatus of the diaphragm, may closely reproduce the substernal oppression and pain of angina pectoris. The pain may be severe and follow a meal; or it may even be referred to the left shoulder region. Epigastric discomfort, heart burn, and eructations of gas should point to the stomach as a possible source of the pain, but diagnosis depends upon fluoroscopic examination.

Gastric and duodenal ulcers rarely cause chest pain, although one occasionally sees patients with an ulcer of the cardiac end of the stomach whose pain is mainly behind the xiphisternum. It has been noted, however, that following a coronary thrombosis, the pain of stomach and gallbladder disease, or of appendicitis, may be referred to the chest and left shoulder.

Palpitation, precordial distress and sometimes substernal pain may accompany *cholecystitis* or *cholelithiasis*. Anginal attacks have been reproduced by pressure on a distended gallbladder, and the not uncommon association of disease of the gallbladder and coronary arteries may add further confusion to the diagnosis.

#### DISEASES OF THE NERVOUS SYSTEM

Pains in the chest of more remote origin than those we have considered are those which come from involvement of the nerve roots of the spinal cord in the thoracic segments. Such root pains may be the sole symptoms, and may at times mislead the most experienced examiner. Once again it seems that their true recognition will follow only when the possibility of

their existence is given consideration. The posterior spinal nerve roots may be involved by pressure from arthritic vertebrae and from spinal cord and nerve root tumors, by caries of the vertebral bodies, metastases to the vertebrae, and by involvement in tabes dorsalis, herpes zoster, multiple neurofibromatosis and toxic peripheral neuritis. Such pains are fairly sharp and shooting, and may encircle the chest in a girdle fashion. Exercise, breathing, swallowing, and the taking of a full meal are not pain-provoking, but movements of the spine, sneezing, and pressure on the vertebral bodies may produce them. Careful examination of the vertebrae for areas of tenderness, tests for spinal mobility and areas of altered cutaneous sensation over the chest should be undertaken with, of course, a complete neurological study and examination of the cerebrospinal fluid.

The pain of *herpes zoster* may be present several days before the appearance of the typical vesicles, and may persist, especially in older people, for many weeks or months following their subsidence. In some cases only two or three small vesicles may be found, in others, they may be clustered in one axilla and readily escape detection. The herpes zoster itself may in turn point to involvement of the posterior spinal root ganglia by leukemia, lymphoma, and other malignant conditions.

Obscure thoracic root pain and paresthesias in elderly people should always lead one to suspect the possibility of *vertebral metastases* from some outlying and perhaps well-hidden carcinomatous focus. Carcinomata of the testes, prostate, lungs, kidneys, thyroid, and breasts are notoriously prone to spinal metastases. Radiography of the spine may reveal hypertrophic arthritis, tuberculosis, myelomatous invasion, Paget's disease, or an old fracture dislocation as the cause of the root pain.

Lastly, we may include in this group the frequent but obscure entities of *intercostal neuralgia*, *bursitis*, *myalgia*, "*pleurodynia*," *mastodynia*, and "*stitch*." Pain aggravated by movement, and tenderness are the only common findings in such cases. Diagnosis is safely made only when the organic conditions outlined above have been excluded.

There must be many instances of chest pain, paroxysmal or persistent, the origin and nature of which are still more

obscure and puzzling. Their elucidation can only follow the conscientious application of known data combined with the alertness that should be a constant trait of the practitioner of physical diagnosis.

### ILLUSTRATIVE CASES

The following cases have been selected as illustrating many of the points alluded to in our introduction.

#### Case I.—Coronary Occlusion with a Minimal Degree of Chest Pain, Very Severe Pain Located in Both Forearms.

B. W., a physician fifty-two years of age, began to suffer from indigestion. He experienced frequent epigastric distress and flatulence, especially at night time. One night he was seized with a sudden severe pain in both forearms which lasted three or four hours. He experienced no chest pain or discomfort. One month later he was again seized with an excruciating "drenching" pain in both forearms, attended by much epigastric discomfort and gaseous eructation, he had no chest pain. The arm pain persisted for ten hours, and during the following four days he developed fever and a moderate leukocytosis. Morphine was required for two days and he remained in bed for eight weeks. On resuming work, typical angina pectoris on effort began, for which he sought relief in the hospital.

His heart was then normal on physical examination and he was in no apparent distress. The blood pressure was 160 mm. of mercury systolic, 100 mm. diastolic. An electrocardiogram showed normal rhythm, rate 90, low T waves in Lead 1, slightly inverted T waves in Leads 2 and 3, with low voltage. He improved and was discharged from the hospital. A few months later another attack of pain in both arms occurred with much shock. A few hours later pain appeared in the chest, the heart sounds became poor, and the blood pressure dropped to 90 mm. systolic and 60 diastolic. Nitroglycerin afforded no relief and morphine was necessary. A pericardial friction rub, a fever of 101° F. for a few days, and leukocytosis (13,000) clinched the diagnosis of myocardial infarction. An electrocardiogram now showed sino-auricular tachycardia, rate 120, low voltage, intraventricular block and a high take-off of the T waves in Leads 1 and 2. Later, the T waves in all leads became inverted.

In this case the main feature was the severe pain in both forearms, later attended by substernal discomfort. Myocardial infarction occurred in one such attack. Cardiac pain may be referred to regions remote from the chest and cause but slight substernal oppression. It thus behooves us to be suspicious of any recurring paroxysm of pain, especially related to exercise, in elderly individuals, or when hypertension is known to be present.

#### Case II.—Gastro-intestinal Pain Complicated by Coronary Pain.

F. M. F., seventy-two years old, a very nervous business man with a his-



tory of indigestion for many years and the development of new symptoms pointing to coronary insufficiency at seventy, had continued for the previous two years to be troubled by both ailments which he himself could readily distinguish. His indigestion had consisted of epigastric and low substernal discomfort associated with belching of gas and what he called "gulping," more often shortly after meals and especially when he ate too heartily or was tired or nervous. He had never had any very severe pain of this sort nor any nausea or vomiting. He had used much bicarbonate of soda and bismuth. Smoking more than his routine three cigars a day after meals or drinking much tea or coffee aggravated the indigestion.

At seventy he rather abruptly developed, while sitting quietly one evening, severe substernal oppression radiating to both arms, this lasted all night and required morphine subcutaneously in the early morning. He remained in bed a few days, feeling fairly well but with a slight fever. Following this illness he had been occasionally bothered by substernal oppression or "clutching" on hurrying. Recently he had been worse, this new symptom being frequently initiated by an attack of indigestion, or vice versa, even when he was quiet. Listening to the radio also sometimes induced an attack. Nitroglycerin quickly relieved the higher substernal oppression and more slowly helped the digestive discomfort with the belching of gas. He could easily distinguish between the two types of symptoms, although they tended often to be superimposed in time, location, and even character. However, the indigestion pain was usually somewhat lower in position, longer in duration, rather more burning in character, more closely associated with eating than with effort, and usually attended by the belching of gas.

Examination revealed a nervous alert man with slight cardiac enlargement, moderate aortic and apical systolic murmurs, accentuated aortic second sound, slight hypertension (170 mm of mercury systolic, 105 mm diastolic), and electrocardiographic evidence of coronary disease (low T waves in Lead I and inverted T waves in Lead 4).

Improvement slowly came with physical and mental rest, reduction of tobacco, sedatives, belladonna, and reassurance. After a few months he was again free from his coronary symptoms, but continued to have his old indigestion and "gulps"\*

This case is representative of a very large group of individuals who have both coronary insufficiency and indigestion. Sometimes the indigestion, which shows itself particularly by the symptom of cardiospasm, has been present for years, as in the present case, before the coronary disease becomes manifest, often, however, it seems to be induced reflexly for the first and subsequent times by the coronary insufficiency, and sometimes the angina pectoris is induced by the indigestion.

\*Still another few months later he was seized by recurrent severe angina pectoris at rest resulting in a few hours in pulmonary edema and death. Autopsy showed extensive coronary disease with narrowing but no obvious acute thrombosis.

Often these cases are very difficult to analyze, but, with care and experience, particularly in dealing with an intelligent patient, there need be little or no confusion in arriving at the correct diagnosis. It must be remembered, incidentally, that the electrocardiogram may show coronary disease without angina pectoris, any symptoms being wholly digestive.

**Case III—Hiatus Hernia Causing Pain Resembling Angina Pectoris**

A G., a man aged forty-four years, complained of bouts of pain in the left upper chest radiating to the left shoulder and arm. Attacks were precipitated by such acts as dressing or walking quickly. At times the pain would persist all day, it was aggravated by exercise. Raising the left arm or lying on the left side bothered him. He experienced some dyspnea on exertion. Nitroglycerin gave no relief. On examination no abnormality could be found in his heart or lungs. Normal blood pressure was found. Electrocardiographic examination and fluoroscopic studies of the heart were normal. Roentgenologic investigation of the stomach revealed a hiatus hernia. A small pouch of stomach could be visualized, wedged into the esophageal hiatus, by manipulation the pouch could be emptied of barium.

Anginal paroxysms can be closely mimicked by several conditions, one of the most elusive of which is hiatus hernia. In this condition a small pouch of stomach near the esophageal opening is wedged upward alongside the esophagus, and presumably by irritation of the diaphragm causes pain which is referred to the left shoulder.

**Case IV.—Radiation of Pain in Coronary Thrombosis Determined by an Active Arthritic Process in the Cervical Spine**

This patient was a man aged fifty years. Six months previously he had begun to suffer from pain in the back of the neck and interscapular region. Arthritic changes in the cervical vertebrae were found on x-ray examination and treatment by exercises and diathermy was instituted. At this time he also began to complain of upper chest pain—not severe, and with no definite relation to exercise. Electrocardiographic examination was normal and some relief was obtained from aspirin therapy and the wearing of a corset. Five months later the patient developed an acute myocardial infarction, with severe substernal pain radiating to both jaws and to the back of the neck. Two weeks later, during convalescence, he experienced further pains, these began in the cervical region posteriorly and radiated downward and anteriorly beneath the axillae to the anterior chest region. Slight fever was associated with this symptom. No evidence of further coronary occlusion could be elicited and the symptoms subsequently subsided. They were no doubt due to the arthritic changes which had caused similar pain at the beginning of his illness.

We know that atypical and bizarre radiation of anginal pain can occasionally be accounted for by the presence of an

adjacent lesion. Moreover, there is clinical evidence that processes arising from such may be exacerbated by the occurrence of paroxysms of anginal pain. In this case the radiation of the cardiac pain and the occurrence of similar pains, in an inverse direction, during convalescence, were in all probability determined by the cervical arthritic process.

**Case V—Arthritis and Coronary Disease Illustrating the Difficulty Frequently Encountered in Elucidating the Cause of Atypical Chest Pain**

This patient, a man, was fifty-two years old. On rare occasions during the past four years he had noticed a slight substernal pain on excessive effort. It would last a few minutes and subside spontaneously. There was no radiation of this pain. Nine months previous to examination he began to notice a more or less constant numbness along the left thumb and radial aspect of the left forearm, this was unrelated to effort. Three months later, after exercising, the numbness increased in severity and spread upward to involve his left shoulder, similar discomfort was experienced over his right shoulder but none over the precordium. Three days later he consulted his physician, who prescribed nitroglycerin. Almost immediate relief of the left arm numbness was obtained, but that in the right shoulder remained unaffected. The patient remained confined to his bed for the next four months and while there experienced occasional severe pain near the right costal margin in the midclavicular line. This was considered to be "intercostal neuralgia."

When seen by one of us he had been up from bed for one month and was working two hours daily. The left arm numbness recurred, but no precordial discomfort was noticed. Severe pain was felt in the mid-dorsal region of his spine and he had to be lifted in and out of his bed for this reason. The left arm numbness was now unaltered by the administration of nitroglycerin. In addition, a moderate degree of swelling of the first and middle fingers of his left hand was observed over the previous four months and some pains were experienced there and in both knees. The patient complained that the pains varied with the weather and that on one occasion his ankles were swollen and painful also. On physical examination his heart showed no abnormalities. By fluoroscopy it was found to be of normal size and shape, and electrocardiographic examination revealed sino-auricular tachycardia, slight right axis deviation, low voltage, upright T waves in Leads 1 and 2, inverted T waves in Lead 3, and normal Lead 4.

No doubt a minimal amount of coronary artery disease with angina pectoris was present in this case, but the majority of the pains experienced were of extracardiac origin and due to arthritis. Irregular relief of the left arm numbness by the administration of nitroglycerin indicated relief of the coronary element but not of the arthritic factor.

*Case VI.—Pulmonary Embolism Simulating Coronary Thrombosis*

C M., a male aged forty-three, was a Swedish-American farmer. He had always led a very strenuous life but had been well except for an injury to his right kidney in a fall at the age of seventeen. He had always worked very hard physically. He used considerable tobacco but very little alcohol.

Six years before our examination he was awakened one morning at 3 a.m. by pain throughout his left chest which was worse on deep breathing and on coughing. This discomfort continued throughout the day and, that evening, he had a second and much more severe pain in the anterior part of his chest, maximally substernal, accompanied by difficult breathing at a rate of 36, considerable cyanosis, and a regular heart rate of 96. He required  $1\frac{1}{2}$  grains of morphine for full relief. He had a slight fever for a few days (rising to 99° F) and a friction rub was heard in the anterior chest on the third day. He remained in bed six weeks and, during the latter part of that time, developed tenderness and swelling of his left leg. His blood pressure was low before, during, and after this attack, dropping to 90 systolic and 60 diastolic at the height of the attack.

Following this illness he increased his activities very gradually over a period of years and resumed his full work on the farm without any ill effect.

Eight months before our examination he experienced a mild pain in his left upper chest without dyspnea or prostration. His first electrocardiogram taken at that time was perfectly normal, including Lead 4.

Four months before our examination he had his second severe attack of chest pain accompanied by rapid breathing and pain in his back on respiration. His temperature rose to 100° F on the third day. His pulse was regular at 72-84. His respirations were 24. The blood pressure was 100 systolic, 64 diastolic. There was a harsh murmur or friction rub over the region of the pulmonary artery, and there was dullness at his right lung base. That same evening he had a much more severe attack of the same type and required morphine twice subcutaneously. An electrocardiogram taken several days later showed no abnormalities, and several weeks later rather low T waves in all leads. After this, the patient made an uneventful convalescence and at the time of our examination showed no abnormality of the heart or lungs, there was, however, slight swelling of the left leg. The blood pressure was normal, 135 systolic, 80 diastolic. Electrocardiographic and x-ray examinations were wholly normal.

This case is an example of what is occasionally seen and often confused with coronary thrombosis, namely, pulmonary embolism from peripheral phlebitis. In this case the phlebitis in the left leg did not appear until after the pulmonary embolism. Such a sequence of events is not unusual, the phlebitis occurring in a deep vein first.

This patient's occupation, unusual dyspnea, pain on breathing with and following the attacks, recurrence of the attacks, relatively negative heart findings during and after them, normal electrocardiograms, pulmonary findings in the form of

friction rub and consolidation, and the involvement of the left leg, established the diagnosis of recurrent pulmonary embolism. We have recommended this patient for study of the left leg venous circulation with the question of ligation of the offending vein to try to prevent further trouble.\* Such therapy has been carried out successfully in a number of cases.

#### SUMMARY

Chest pain can be a very complicated symptom because of the many possible causes for such pain and the similarity in site, character, duration, and circumstance of several of the different varieties of chest pain.

The most common causes of chest pain are, in the order of their occurrence: strain or injury of the chest wall itself, indigestion, with spasm of the esophagus and cardiac end of the stomach, pulmonary and pleural involvement, gallbladder disease, and coronary insufficiency in the form of angina pectoris or coronary occlusion. Rarer causes of chest pain are pressure from or rupture of saccular aneurysms, dissecting aneurysms, spontaneous pneumothorax, spontaneous mediastinal emphysema, thoracic tumors, spinal disease, and herpes zoster.

\* This was later carried out, an extensive deep phlebitis being found.

## CLINIC OF DR SOMA WEISS

FROM THE PETER BENT BRIGHAM HOSPITAL AND THE DEPARTMENT OF MEDICINE, HARVARD MEDICAL SCHOOL

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### DISEASES OF THE HEART AND THE AORTA WHICH ARE NOT WELL RECOGNIZED

IN the daily practice of medicine, one encounters disorders of the heart and of the aorta which cannot be classified as any of the common diseases of these organs. Such cases are not frequent, but neither are they rare. Without a critical attitude, one is likely to conclude that these patients are suffering from common diseases of the heart and of the aorta. The diagnoses usually made in these instances are arteriosclerotic, hypertensive, rheumatic, or congenital heart disease.

Such clinical diagnoses are usually accompanied, however, by a feeling of uncertainty. One is likely to acknowledge that in these cases the specific etiologic factors of the diagnosed disease are lacking, that the symptomatology and other features of the case do not correspond to any of the common disorders of the heart or of the aorta, and that the labeling of the case has been "forced" and somewhat arbitrary. It is this attitude of forcing cardiac disorders into a limited group of recognized diseases which handicaps further progress in the etiologic classification of cardiac diseases.

While the number of cases of each of the usually unrecognized diseases of the heart and of the aorta is small, the total number of these diseases represents a large group of patients, whose condition is obscure to, or inadequately understood by, the physician. It is the purpose of this clinic to call attention to the general significance of this group without entering into details.

Our attention has been called to this problem during the course of studies on beriberi heart disease,<sup>1 2</sup> myocardial abscess,<sup>3</sup> dissecting aneurysm of the aorta,<sup>4 5</sup> and gummatous

aortitis<sup>6</sup> In the diagnostic selection of these cases for special studies, we have encountered a number of other obscure conditions, which had to be differentiated from those investigated by us Dr von Bonsdorff subsequently undertook a systematic analysis of the obscure and less common causes of heart disease on the basis of a study of 6330 consecutive autopsies on patients of all ages in the Boston City Hospital from the years 1928 to 1938<sup>7, 8, 9, 10</sup> Extensive literature may be found in his publications

#### A COMPARISON OF THE WELL RECOGNIZED DISEASES OF THE HEART AND OF THE AORTA WITH THOSE WHICH ARE NOT WELL RECOGNIZED

The general significance of this problem can be demonstrated in a simple manner, by means of a comparison of a tabulation of the well recognized and common diseases of the heart and the aorta with that of the less common and obscure diseases of these organs

##### *I A Well Recognized Diseases of the Heart*

- Congenital cardiac defects
- Rheumatic heart disease
- Syphilitic heart disease
- Acute and subacute bacterial endocarditis
- Heart disease in infections (diphtheria, scarlet fever, streptococcus sepsis, tuberculosis, etc.)
- Heart disease in thyroid disease
- Heart disease in arterial hypertension
- Cor pulmonale
- Coronary insufficiency (sclerosis and thrombosis)
- Constricting pericarditis (tuberculosis, etc.)
- Neurocirculatory asthenia

##### *B Not Well Recognized Diseases of the Heart*

- Thoracic and spinal deformities
- Arteriovenous aneurysm
- Disorders of nutrition (obesity, hydremia, anemia, beriberi, rickets, scurvy, starvation)
- Hepatic cirrhosis (pancreatitis?)
- Glycogen disease (von Gierke's)
- Amylodosis
- Xanthomatosis
- Hyperproteinemia (?)
- Hypoglycemia
- Tetany
- Familial periodic paralysis

Pituitary disease (acromegaly)  
 Congenital idiopathic hypertrophy of the myocardium  
 Extrinsic poisons (bichloride of mercury, barbiturates, nicotine, digitalis, carbon monoxide, etc.)  
 Trauma (concussion of the heart)  
 x-Rays and electric current  
 Glomerulonephritis  
 Toxemia of pregnancy  
 Idiopathic postpartum failure of the heart  
 Lupus erythematosus disseminata  
 Periarteritis nodosa  
 Boeck's sarcoid  
 Thrombo-angitis obliterans  
 Serum carditis (?)  
 Influenza and other respiratory infections  
 Anterior poliomyelitis  
 Acute syphilitic myocarditis  
 Gummatous myocarditis  
 Myocardial abscess  
 Trichiniasis  
 Obscure ("Fiedler's") myocarditis of infectious origin  
 Neoplastic infiltration of the heart  
 Cerebral causes of organic character (trauma, tumor, epilepsy)  
 Cerebral causes of psychic nature  
 Carotid sinus and other cardiac reflexes (gallbladder disease)  
 Polyneuritides  
 Progressive muscular dystrophy  
 Friedreich's ataxia

## II A *Well Recognized Diseases of the Aorta*

Congenital defects  
 Syphilitic aortitis and aneurysm  
 Arteriosclerosis (aneurysm)  
 Rheumatic aortitis

## B *Not Well Recognized Diseases of the Aorta*

Dissecting aneurysm  
 Gummatous aortitis  
 Acute infections (abscess)  
 Mycotic aneurysm  
 Rheumatic aneurysm (?)  
 Tuberculosis  
 Aortitis of undetermined origin

An analysis of the tabulations presented reveals (1) The usually not well recognized diseases of the heart and of the aorta are actually *greater in number* than those which are recognized (2) The obscure groups represent partly *functional* (reversible) and partly *organic* (irreversible) diseases, the latter being more frequent (3) The unrecognized dis-



eases of the heart represent *nonvalvular* disease or irritability of the myocardium (4) The myocardial failure is the result of either (a) intrinsic or extrinsic noxious factors acting *directly* on the myocardium or on the coronary vessels, or (b) causes affecting primarily some other parts of the circulatory system and, in turn, indirectly increasing the burden on the heart (5) These diseases are *mechanical, metabolic, extrinsic poisonous, physical, anaphylactic, infectious, neoplastic, or neurogenic* in origin

I shall comment briefly on these diseases, hoping that these general remarks and the scattered references cited will be of help to physicians in recognizing the conditions with increasing frequency

#### COMMENTS ON THE NOT WELL RECOGNIZED DISEASES OF THE HEART

**Thoracic and Spinal Deformities** —The relation of these deformities and particularly of right-sided dorsal kyphoscoliosis to dyspnea, limitation of physical activity, heart failure, and early death has been described in several classical publications of the German and French schools of the nineteenth century The danger of pulmonary infections in such patients is also known by experienced physicians American physicians have neglected the study of these cases The recent investigation of Chapman, Dill, and Graybiel<sup>11</sup> contains valuable information on the clinical as well as the physiologic characteristics of this disease

**Arteriovenous Aneurysm.**—The arteriovenous communication, whether it is congenital or acquired, if of sufficient size, can lead to embarrassment of the heart and eventually to heart failure In an arteriovenous aneurysm of several years' duration, there develops not only dilatation of the cardiac chamber, but also hypertrophy of the myocardium This type of heart failure is an example of the effect on the heart of reduced peripheral vascular resistance, such as is also present in thyrotoxicosis, fever, and beriberi Surgical treatment of arteriovenous aneurysm may reestablish good cardiac reserve even after complete debility of years' duration The physiology involved in this disturbance of the circulation and the symptomatology of the disease have been discussed in the literature<sup>12</sup>

**Disorders of Nutrition**—Malnutrition contributes in a significant way to disturbed heart action, including myocardial failure. Factors directly affecting the heart, as well as indirect factors changing the peripheral vessels or composition of the blood, are operative here.<sup>13</sup>

Among the various types of avitaminosis, lack of vitamin B<sub>1</sub> plays the most important rôle. That beriberi, both of the alcoholic and of the nonalcoholic type, is a regular occurrence not only in this but also in other parts of the world is indicated by reports from the Orient as well as from Sweden, Holland, France, Great Britain, Germany, Labrador, and South America. Several of these reports describe the efficacy of thiamin or food rich in vitamin B<sub>1</sub> in the treatment of this form of heart disease. The diagnosis of beriberi heart disease can be made with a fair degree of probability.<sup>13 14</sup>

Whether types of avitaminosis other than B<sub>1</sub> deficiency can lead to myocardial failure is not established with certainty. Myocardial failure has been described in children with scurvy and with rickets. There is a probability that in these cases multiple deficiency, including vitamin B deficiency, was operative.<sup>13</sup> Pericardial hemorrhage with effusion can develop in instances of severe scurvy. Further knowledge is needed on the interaction of various types of vitamin deficiencies as well as on the bodily effects of a combination of certain types of avitaminosis with other types of hypervitaminosis. Obviously man seldom chooses his food so that it is lacking in but one vitamin.

*Anemia* may be responsible for myocardial dilatation and weakness. These changes are associated with changes in the electrocardiogram. In severe anemia of long duration, myocardial hypertrophy may develop. In anemia the primary etiologic factor is myocardial anoxia, yet in many instances of primary and secondary anemia we are dealing also with multiple nutritional deficiency. Hence in the treatment of these patients, improvement of the anemia alone is not adequate. Vitamin-rich diet should be used in addition to the specific treatment for the anemia.

At present there is no definite evidence that *hypervitaminosis* of any type damages the heart. In animals, large doses of vitamin D produce a certain type of arteriosclerosis, which may involve also the coronary arteries. The clinical evidence,

however, for the existence of myocardial failure in infants who have received large doses of vitamin D (ergosterol) is not convincing

It should be recalled that *obesity* is an important factor in interfering with the efficiency of the cardiovascular system. In this nutritional disorder indirect factors affecting the function of the diaphragm, the vital capacity of the lungs, the peripheral vascular resistance, and the venous return of the blood to the right side of the heart are far more important than the direct effect of corpulency on the myocardium through fatty ingrowth. Careful regulation of weight, in the male as well as in the female, would add greatly to the "cardiac efficiency of the nation."

**Hepatic Cirrhosis**—Patients with hepatic cirrhosis suffer at times from circulatory insufficiency as well as from myocardial failure. The mechanism of this failure is not always clear. It is certain, however, that the disturbed cardiovascular functions associated with cirrhosis of the liver are *not* all of the same etiology. Circulatory embarrassment, including dyspnea and high venous pressure, may be the result of the mechanical effect of severe ascites. Hydrothorax is also likely to be present, due in part to low serum protein.

In one group of patient with cirrhosis, vitamin B deficiency also plays a rôle. In the Laennec ("alcoholic") type of cirrhosis, I have observed myocardial failure without the presence of any of the above-mentioned factors. One wonders whether in these latter instances disturbance of the intermediary metabolism or lack of proper utilization of food is not the responsible factor. In 2 cases with severe hemochromatosis and heart failure, without nutritional deficiency, observed by us there was free deposition of pigment in the myocardium.

The French writers have described a type of heart disease (the endocrine-hepatocardiac syndrome) in patients with hemochromatosis. Endocrine disturbances, including infantilism, are claimed to be present in these cases. The heart is enlarged, the blood pressure is normal. There may be gallop rhythm and changes in the electrocardiogram. It is of interest that of 38 cases with hemochromatosis in the Boston City Hospital the heart weights of 16 were more than normal. It is of practical importance to emphasize that in patients

with heart disease associated with cirrhosis of the liver, usually several of the factors described are operative

von Bonsdorff has reported<sup>9</sup> a case, which I have studied in which severe myocardial failure developed shortly postpartum and which was associated with acute pancreatitis and hypocholesteremia. The nature of this case has not been clear to me

**Hyperproteinemia, Amyloidosis, and Xanthomatosis of the Heart**—Rarely these disturbances of the metabolism may be responsible for cardiac disturbances. The rôle of *hyperproteinemia* as a causative factor in heart failure is not established definitely. von Bonsdorff et al.<sup>15</sup> have studied a man, aged thirty-six, with myeloma, in whose blood large amounts of crystallizable, high molecular, viscid protein was present and in whom subsequently severe congestive failure associated with rapidly increasing size of the heart developed. Both digitalis and vitamin B<sub>1</sub> were ineffective. None of the common causes of heart disease was present. The influence of blood with high protein-content on the heart, therefore, requires further elucidation.

*Amyloidosis* is one type of disturbance of the protein metabolism. Deposition of amyloid in the myocardium is not rare. At times, particularly in elderly patients, deposition of amyloid in the heart may be the only manifestation of amyloidosis. *Cardiac amyloidosis* is, however, responsible for myocardial failure in only a small number of the total group. The clinical diagnosis of these cases is difficult, but can be suspected.

*Generalized xanthomatosis* with hypercholesteremia is relatively frequently associated with cardiac lesions, but seldom with failure of the heart. Such depositions may be responsible for aortic stenosis and obstruction of the coronary arteries.

**Glycogen Disease (von Gierke)**—Intracellular accumulation of glycogen can cause cardiac hypertrophy and myocardial failure, particularly in children and young adults. Some of the cases of so-called idiopathic congenital hypertrophy of the heart of early childhood belong in this group. This affection of the heart comprises but a small number of these young patients with obscure myocardial failure.

**Hypoglycemia**—Low blood sugar, in addition to causing

circulatory collapse, may be responsible for usually transient irregularities of the heart. In my experience these cardiac difficulties are likely to occur in elderly patients with coronary disease. There is no indication that hyperglycemia *per se* is responsible for cardiac embarrassment.

**Tetany**—This may be associated with tachycardia or bradycardia. More rarely, angina pectoris-like attacks develop. Auricular flutter, lengthening of the electrical systole, changes in the Q and T waves, and other intracardiac abnormalities have been described. These disturbances disappear after the administration of calcium. Sudden cardiac death also occurs in rare instances.

**Familial Periodic Paralysis**—These patients sometimes exhibit transient cardiac irregularities during attacks. There may also be split first sound, transient systolic murmur, and increase in the cardiac dullness. Electrocardiographic changes may develop during the attacks. I have had an opportunity to observe such electrocardiograms in one case. Holtzapfle, as mentioned by von Bonsdorff, has witnessed acute cardiac death in one case.<sup>8</sup> There was terminal pulmonary edema, as a result of acute myocardial insufficiency. The relation of low potassium-content of the blood serum to these cardiac disturbances, as well as the therapeutic influence of potassium, dextrose, and choline derivatives, awaits further investigation.

**Pituitary Disease (Acromegaly)**—Certain disorders of the pituitary gland *per se*, irrespective of the occasionally associated hypertension, may apparently be responsible for myocardial hypertrophy and heart failure. French clinicians have written rather extensively on this subject. It is assumed by most observers that the cardiomegaly is but a part of the general splanchnomegaly present in this disease. In the American literature, Courville and Mason<sup>16</sup> have recently discussed this remarkable but still obscure condition. This important problem needs further clarification.

**Congenital Idiopathic Hypertrophy of the Myocardium**.—Although this condition has been recognized for a long time, the nature of the disease remains obscure. It probably represents several different types of disturbance of the heart in early childhood. Glycogen (von Gierke's) disease accounts for only a small percentage of the cases. I have

seen instances of idiopathic myocardial hypertrophy in which the coronary vessels were underdeveloped, and the question has been raised whether chronic cardiac ischemia was not responsible for the condition. Attention should be paid in the future to the possible effect on the myocardium of the infant of respiratory infections of the mother during pregnancy, as well as of respiratory infections of the newborn. The serious character of this heart disease is known.

**Extrinsic Poisons**—A number of chemical substances of extrinsic origin exert a harmful effect on the heart. Many of these are therapeutic agents, but in large doses, particularly after prolonged use, they exert a harmful effect on the myocardium. This problem is an important one, and one which requires further study in order that the practitioner should be able to guide his patients better.

In the present era of industrialization, there is increasing opportunity for workers to be exposed to such chemical substances. This fact, together with the possibility of an increasing use of chemicals in *wars of the future*, indicates that *this chapter of medicine will probably increase in significance*. The effect of *nitroglycerin, dinitrophenol, and related substances* in causing sudden and almost mysterious death, with or without premonitory attacks of angina pectoris, has been observed extensively among munition-workers.

The harmful effect of *chloroform*, particularly on the already damaged heart, brings about cardiac injury.

It is known that *epinephrine* can cause various types of cardiac arrhythmias and angina pectoris, with or without pulmonary edema, particularly in the presence of various diseases, including coronary insufficiency and myocarditis. On the other hand, the prolonged use of epinephrine in patients with asthma or giant urticaria does not cause (with very rare exception) chronic myocardial or coronary disease.

*Mercury chloride*, if ingested in massive doses and particularly if it is absorbed rapidly from the stomach (usually through an eroded blood vessel), causes myocardial weakness, as also manifested by electrocardiographic changes. Death in these patients occurs relatively rapidly, and this is due to myocardial failure and not to uremia.

*Digitalis* can be responsible for myocardial insufficiency and for transient arrhythmias if taken in large doses. I have

had occasion to observe the harmful effects of digitalis in ambulatory patients who, as the result of insufficient or incorrect instruction on the part of physicians, consumed large doses of the drug over a long period. At times it is surprising to learn the large amounts of digitalis which have been taken by these patients.

*Ergotamine* can precipitate cardiac asthma in patients with hypertension.

The *barbiturates* in toxic doses affect myocardial efficiency. When they are administered in large doses to animals, impairment of cardiac reserve can be clearly demonstrated. Large doses of the barbiturates cause disturbance of the pulmonary circulation, as manifested by pulmonary hypostatic congestion or pulmonary edema in man. It is for this reason that these patients have a pronounced tendency to develop bronchopneumonia or lobar pneumonia.

*Carbon monoxide* poisoning may be associated with cardiac lesions in a small number of cases. Changes in the cardiac rate and rhythm, and dilatation of the heart with changes in the electrocardiogram, can occur. Whether all these changes are the result of cardiac anoxia or whether in addition injury to midbrain centers plays a rôle in the impaired cardiac function is not known.

The harmful effect of smoking in some persons is recognized, but it is still not known definitely which constituents in the *tobacco* or the paper of cigarettes are the most potent factors.

Consumption of large amounts of *caffeine* or related substances may be responsible for an irritable heart. The possible relation of smoking and consumption of tea and coffee to coronary disease, including thrombosis, is a problem that merits investigation.

The possible harmful effect on the heart of a number of other substances (bromides, iodides, acetanilid, etc.) is not established because of lack of sufficient clinical and experimental data on the subject.

**Trauma (Concussion of the Heart).**—Blunt traumatic injuries of the thorax can be responsible for myocardial failure. Patients with preexisting heart disease are, in my experience, particularly sensitive to such thoracic injuries. I have observed instances in which severe injuries of the thorax with-

out direct contact with the heart have been associated with multiple minute myocardial hemorrhages. This is not always the case, however, in concussion of the heart. It has to be acknowledged that the diagnosis of "concussion of the heart" is difficult, because other etiologic factors have to be weighed carefully. Recently Warburg has discussed this problem extensively.<sup>17</sup>

**x-Rays and Electric Current**—The effect of these forms of physical energy (x-ray and radium) on the heart is not established as yet. The available reports in the literature are not convincing. Electric current can produce dilatation of the heart.

**Glomerulonephritis, Toxemia of Pregnancy, and "Idiopathic" Postpartum Myocardial Failure**—There appears to be a certain degree of similarity between these types of cardiac disturbances. In *glomerulonephritis*, manifestations of circulatory failure are not uncommon. Lowered vital capacity of the lungs, dyspnea, with or without high venous pressure, and tendency to paroxysmal attacks of dyspnea are relatively frequent in acute and subacute glomerulonephritis. These changes can develop independently of hypertension, and therefore cannot always be attributed to it.

It is probable that the tendency to water-retention and the increase in the circulating blood volume are causative factors, and these explain in part the pronounced tendency to pulmonary congestion and edema. In some of the cases, however, there is direct involvement of the myocardium, which is again independent of a coexisting hypertension. Transient or permanent changes in the electrocardiogram also support such a contention.

The cause of this myocardial failure in glomerulonephritis is not clear. There is a possibility that, as in beriberi heart disease, with which the clinical features of myocardial disease of glomerulonephritis have much in common, chemical changes in the blood or the vessels are the primary factors, and these affect the myocardium secondarily. The possible effect of hormones requires investigation. Whitehill, Longcope, and Williams<sup>18</sup> have recently reported on this problem.

In severe cases of *toxemia and eclampsia*, manifestations of circulatory failure are not rare. The literature on this subject is confusing, and careful observations are still lacking. Judg-



ing from personal experience, the majority of instances of heart failure in toxemia and eclampsia are related primarily to acute and severe hypertension. There is, however, one additional factor, namely that of water-retention (including that in the lungs), which results in an embarrassment of the pulmonary circulation, which in toxemia and eclampsia is out of proportion to the severity of hypertension.

In toxemia and eclampsia there is a great tendency to cardiac asthma and to pulmonary edema. Rarely, one observes cases in which the myocardial failure cannot be explained on the basis of these factors alone. One wonders whether abnormal activity of the glands of internal secretion is not responsible for these instances.

The occurrence of "*idiopathic*" or "*toxic*" myocardial failure during and after pregnancy, not associated with glomerulonephritis or with toxemia of pregnancy, represents an interesting group of cases. These cases must not be confused with heart disease of nutritional disorders (beriberi), or with other recognized types of heart disease which tend to become aggravated toward the end of pregnancy.

In the classical case we are dealing with a formerly healthy young woman who, towards the end of pregnancy or more frequently shortly after delivery, develops progressive myocardial failure without evidence of hypertension or coronary disease. The usual features are gallop rhythm, dyspnea, cardiac enlargement, edema, and engorgement of the veins. Embolism may complicate the course of this illness. The disease is usually benign with recovery, but it can cause prolonged incapacity and may also terminate fatally. There is no therapeutic response to vitamin B<sub>1</sub>, and a rather unsatisfactory response to digitalis. Histologic examination may reveal either no myocardial changes, or "interstitial edema," parenchymatous degeneration, or necrosis. Endocardial thrombi may also be present.

Unfortunately in the few reports in the literature, including the important contributions of Hull and Hidden<sup>19</sup> and Gouley, McMillan, and Bellet,<sup>20</sup> several of the different types of rare and obscure myocardial failures that may occur in pregnancy are not clearly differentiated. Whether this type of heart failure is infectious or metabolic in origin, and whether it has any relation to the group discussed under "Respiratory

Infections" and "Fiedler's Myocarditis," is not clear to the writer

**Lupus Erythematosus Disseminata**—In this disease myocardial failure of varying degrees is rather common. At times the skin manifestations may be slight, preterminal, or even completely absent, and the heart failure dominates the picture. Dyspnea, precordial distress, cardiac enlargement, pulmonary congestion, pleural transudate or exudate, and pericardial or pleuropericardial friction rubs were the usual symptoms and signs in the cases personally observed. The myocardial failure may be associated with pericardial effusion or adhesive pericarditis or mediastinitis. Cardiac irregularities and electrocardiographic changes may be present. Histologic examination may reveal either no changes, or "interstitial edema," scarring, and at times thrombosis of the coronary arterioles. These cases are likely to be misdiagnosed as rheumatic fever or infectious arthritis with cardiac involvement, or as various types of obscure myocarditis. At times they are described as new syndromes.

**Boeck's Sarcoid.**—This condition was considered a skin disease for a long time following the early descriptions of the disease by Hutchinson in 1869, Bernier in 1889, and Boeck in 1899. Visceral involvement including lungs, intestine, liver, spleen, bones, kidney, prostate, and epicardium have been described. More recently a few cases have been reported with myocardial and endocardial involvement.

The most recent and remarkable case with extensive myocardial involvement is that reported by Cotter<sup>21</sup>. The clinical course of this eighteen-year-old Negro was rapid, progressive myocardial failure, with dyspnea, orthopnea, edema, and cough. The heart was enlarged. The rate was rapid, and the second sound at the pulmonic area was accentuated. The electrocardiographic picture changed from that of sinus tachycardia with arborization block and low voltage to that of auricular fibrillation, complete heart block, and a shifting pacemaker. On postmortem examination the heart weighed 450 gm. All chambers were dilated. The myocardium had been extensively replaced by chronic inflammatory granulation tissue, in which there was fibrosis, but no caseation.

**Periarteritis Nodosa**—This disease very rarely may involve branches of the coronary arteries and can thereby cause

cardiac embarrassment In one case, with whose history I am familiar, there was a diffuse involvement of the small arteries of the pulmonary vessels and, as a result of it, the disease imitated the picture of miliary tuberculosis

**Thrombo-angutis Obliterans**—Seldom the coronary arteries can become involved, leading to thromboses, in this disease The corresponding clinical picture is that of myocardial failure

**Serum Carditis**—There are few suggestive reports in the literature indicating that following the administration of sera and after anaphylactic phenomena cardiac embarrassment and even death followed Proliferation of histiocytes in the endocardium and acute proliferative changes in the branches of the coronary arteries have been described I had no opportunity to observe such cases

**Influenza and Other Upper Respiratory Infections.**—Temporary insufficiency of the heart following attacks of influenza is common It is more surprising to find, however, that an apparently mild attack of upper respiratory infection can at times be followed by severe, or even permanent, damage to the myocardium The exact differentiation of the cardiac effects of various types of upper respiratory infections is not feasible at present This group of patients with heart disease represents *a problem of real practical significance* The separation of this myocardial failure from the so-called Friedler's myocarditis is not feasible at present

In the majority of instances, the cardiac disturbances following upper respiratory infection are transient and functional in nature They may be associated with disturbances of the intracardiac conduction and changes in the heart rate and rhythm The heart becomes irritable Only seldom does sudden death in otherwise robust persons occur

It is probable that some of the instantaneous deaths after strenuous athletic exertion in robust persons, in whom post-mortem examination fails to reveal any recognized cause of death, fall into this group Egedy has stated<sup>22</sup> that about 20 per cent of all influenza patients develop symptoms of heart disease, and in about half of these cases changes in the electrocardiogram are present The relative frequency of cardiac involvement varies in different epidemics<sup>22a</sup> Recovery may be rapid or protracted Histologic changes in the myocardium have been found in but a small group of the cases<sup>21</sup>

I have had opportunity to observe a group of patients, usually young adults and children, who after an attack of apparently innocuous bronchitis rapidly developed severe myocardial changes, leading to congestive failure. Gallop rhythm, heart block, pulsus alternans, and fibrillation are frequently present. Evidence of valvular disease is lacking. After a lapse of several months there is improvement, but more frequently permanent damage is the final outcome. These patients eventually become cardiac invalids.

It is of interest that in a recent report on anatomic findings in patients after sudden death, Lisa and Hart<sup>24</sup> point out the frequency of respiratory infections associated with myocarditis. Whether in these cases there is a more severe cardiac effect of usual respiratory infections, or a specific infection is involved, is not known at present. The clinical picture somewhat resembles rheumatic fever with cardiac complications, with which condition this disease is usually confused.

**Anterior Poliomyelitis**—von Bonsdorff<sup>8</sup> has described morphologic lesions in a small group of cases with anterior poliomyelitis. Hemorrhages, necroses, and parenchymatous degeneration were present in the myocardium. The mechanism and the significance of these lesions are not clear. Neurogenic, specific myocardial, or nonspecific concomitant factors are the possible causes in the pathogenesis. At present there is no evidence, however, that anterior poliomyelitis can be responsible for chronic heart disease.

**Syphilitic Myocarditis**—During the secondary stage of syphilis, transient cardiac disturbances may be present. These are usually mild and manifest themselves in cardiac irregularities. Gummatous myocarditis is a rare occurrence, and the diagnosis of this condition is difficult.

**Myocardial Abscess**—This condition is usually a manifestation of staphylococcus sepsis. In rare instances, however, solitary myocardial abscess may develop, and this eventually may rupture into the pericardial sac or into cardiac cavities. In very rare cases, cardiac murmurs may develop, imitating valvular heart disease, when the myocardial abscess penetrates the endocardium. The clinical features and significance of this condition have been discussed elsewhere.<sup>3</sup>

**Trichiniasis**—This infestation can cause myocardial weakness, with or without cardiac arrhythmias and electro-

cardiographic changes Spink<sup>25</sup> has studied this aspect of trichiniasis on the clinical material of the Boston City Hospital and demonstrated that the trichinae can infest the myocardium

**Obscure (Fiedler's) Myocarditis of Infectious Origin.**—In 1899, Fiedler described a myocarditis associated with lymphocytic infiltration. This myocarditis occurred in young people who suffered from mild and vague infections of non-specific nature. At postmortem the only demonstrable organic lesions were found in the myocardium. Usually lymphocytic infiltration with plasma and polymorphonuclear cells was present.

The significance of this condition has been discussed repeatedly in the literature without any further clarification of the problem. Scott and Saphir<sup>26</sup> have recently reviewed the literature. The patient is usually between the ages of twenty and fifty. Tachycardia with gallop rhythm, irregularities, and electrocardiographic changes are frequent. Cardiac embarrassment and congestive failure develop slowly, but at times they occur quite abruptly. Improvement may be slow. The condition can be fatal. Pulmonary and peripheral embolism can complicate the clinical picture as a result of dislodging of endocardial thrombi. This and other features of the disease usually raise the diagnostic possibility of "silent" coronary thrombosis or atypical rheumatic carditis. This condition exists, as judged from my experience, and it is similar to or identical with the myocardial changes observed after various types of respiratory infections (p 1336). This type of myocardial failure may bear a close relation also to idiopathic cardiac hypertrophy of infants or children.

**Neoplastic Infiltration of the Heart**—In recent years, increasing attention is being paid to these lesions of the heart. The diagnosis of primary and secondary tumors of the heart is made with greater frequency. Metastatic tumors of the heart are by far the most frequent. In the majority of instances, the infiltration is direct, usually from neighboring structures such as the lung, pleura, mediastinum, or via the vena cava. Affections of the right side of the heart are more common. Often the cardiac neoplasm gives no symptoms or signs. When, however, there is unexplained cyanosis, attacks of syncope, cardiac irregularity, and electrocardiographic

changes during the course of neoplastic diseases, which are apt to metastasize or are located near the heart, the probability of neoplastic infiltration of the heart may be suspected

**Cerebral Causes of Organic Nature**—Experimental stimulation of the hypothalamus can produce premature beats of the heart. Blows to the heads of animals can cause cardiac irregularity and changes in the electrocardiogram. I have observed at times similar changes in man, following fracture of the skull. In patients with brain tumors, changes in cardiac rate and elevation of the blood pressure frequently develop. Rarely, severe fluctuation of the arterial pressure with tendency to dyspnea occurs, without obvious reason in patients with cerebral neoplasms. The clinical picture of these cases can closely simulate that of paroxysmal hypertension of chromaffin tumor origin. In one such case, observed through the kindness of Dr E Sachs, of St Louis, temporary blindness, dyspnea, and orthopnea were associated with each of the many paroxysmal elevations of the arterial pressure. Reports are also available indicating that brain tumors can be associated at times with subendocardial hemorrhages. The significance of these reports is not clear to me.

**Cerebral Causes of Psychic Nature**—Emotions can exert significant influence on the function of the heart. Because the diseased heart is usually hyperirritable, the rôle of emotional factors can become of paramount importance. The proper recognition of this has an important bearing on treatment. In the precipitation of various types of cardiac disturbances, physiologic mechanisms of definite patterns are operative. This has been discussed in detail elsewhere.<sup>27</sup>

**Carotid Sinus and Other Cardiac Reflexes**—A hyperactive carotid sinus as well as reflexes originating from other areas, such as the eyeball, esophagus, stomach, gallbladder, and other organs, can precipitate functional disturbances of the heart, including arrhythmias. Dizziness, weakness, and syncope can be associated with the attacks. The details of these clinical syndromes have been described.<sup>28, 29, 30, 31</sup>

**Polyneuritides**—In the dry neuritic form of beriberi, both of the alcoholic and of the nonalcoholic type, tachycardia and electrocardiographic changes can be present. Similarly, in other types of severe polyneuritides, tachycardia is not uncommon. The pathogenesis of the cardiac disturbances asso-

ciated with these polyneuritides is not clear. In the cases of neuritic beriberi associated with tachycardia and other circulatory changes studied by us, histologic alteration in the vagus nuclei was found.

It has been suggested in the past that "vagus neuritis" may be responsible for these cardiac disturbances (Shimazono). Whether through the pathology of the cardiac nerves secondary humoral factors are operative, such as have been found in the experimental work of Banting, Hall, and their associates, is not known at present.

**Progressive Muscular Dystrophy**—These patients at times suffer from attacks of tachycardia and, rarely, they die suddenly. Electrocardiographic changes have also been described. Whether these changes depend on organic changes in the myocardium, similar in nature to those occurring in the voluntary muscles, or the cardiac disturbances are the result of secondary influences, is discussed in the literature.<sup>32, 33</sup>

**Friedreich's Ataxia**—This familial disease may be associated with heart disease, as reported by French physicians<sup>34, 35, 36</sup>. Tachycardia, premature beats, auricular flutter, and fibrillation can occur. Rarely, congestive failure follows. The electrocardiogram may show prolongation of the P-R and Q-R-S intervals, changes in the shape of the S-T segment, and low voltage. Postmortem reports have described cardiac enlargement and histologic alterations in the myocardium. I have not seen instances of cardiac disturbances in Friedreich's ataxia.

#### COMMENTS ON THE NOT WELL RECOGNIZED DISEASES OF THE AORTA

The clinical significance of this group of diseases is distinctly less than that of the heart. These conditions occur relatively rarely and, even if they are clinically recognized, usually little can be done, except in gummatous aortitis, to alter the condition of the patient. In the majority of instances the conditions are of only morphologic interest.

**Dissecting Aneurysm**—The morphologic characteristics of this condition have been known for a long time, but it is only in recent years that the clinical characteristics of dissecting aneurysm have been formulated. With the aid of this clinical knowledge a large percentage of the cases can be diag-

nosed The preëxisting hypertension and arteriosclerosis, the sudden onset, the character of the pain, and the bizarre, scattered signs depending on obstruction or dissection of arteries are the diagnostic characteristics x-Ray of the chest is frequently helpful

It has been pointed out that the frequency of this condition in the Boston City Hospital is increasing It is probable that with the decreasing incidence of syphilis and with the progressive prolongation of life and the resulting increased incidence of degenerative disease, dissecting aneurysm will soon be a more frequent disease than syphilitic aneurysm Thus this disease is no more a mere anatomic curiosity The clinical characteristics and vagaries of this condition have been described elsewhere <sup>4 5</sup>

**Gummatous Aortitis**—While the scar-forming type of chronic aortitis is common, gummatous aortitis is relatively rare In an analysis of some 300 cases of syphilitic aortitis, gummatous aortitis was present seven times <sup>6</sup> The symptomatology of these cases does not differ from cases of chronic aortitis In one case, recently studied with Dr F Parker, Jr, however, as a result of diffuse gummatous infiltration of the pulmonary artery and the aorta, sudden death developed

**Acute Infection (Abscess).**—These lesions are rare and usually develop as a result of sepsis Preëxisting lesions, particularly arteriosclerosis, predispose to bacterial invasion of the intima

**Mycotic Aneurysm.**—In association with bacterial endocarditis, mycotic aneurysm of the aorta can develop These aneurysms are usually small, and they seldom rupture Recently an unusual case of this type has been observed A male, aged forty-one, suffered from a febrile disease of one month's duration The nature of the aortic valvular lesion was not clear during the life of the patient The patient temporarily responded favorably to sulfanilamide treatment, but subsequently the fever returned

Before death two positive blood cultures yielding gonococci were obtained At postmortem the stenotic aortic valve showed evidence of healing About 4 cm above the aortic valve there was a small saccular aneurysm containing vegetation This small aneurysm had perforated The interpretation of the case was that the patient had suffered from gonococcus



endocarditis with mycotic aneurysm of the aorta. The original site of the infection at the aortic valve had healed, but the metastatic infection in the aneurysm remained progressive.

**Rheumatic Aneurysm.**—The existence of this condition may be considered as questionable. I have observed two post-mortem specimens, one with small aneurysm of the ascending arch, the other in the abdominal portion of the aorta. Both occurred in youthful patients with rheumatic carditis. Syphilis or other infections were not present.

**Tuberculosis**—This is a rare lesion. It usually occurs from extension of the tuberculous process from neighboring structures.

**Aortitis of Undetermined Origin**—Cases are observed rarely in which, on postmortem examination, aortitis of undetermined origin is found.

### CONCLUSIONS

1 The purpose of this clinic was to demonstrate and emphasize the fact that there exists a large group of patients who suffer from diseases of the heart and of the aorta which usually are not recognized by physicians. The available knowledge on some of these diseases is adequate, but this has not penetrated as yet the sphere of routine diagnostic considerations. Information on other of these disorders, however, is still meager.

2 In several of the cardiac disturbances discussed, the pathogenesis is psychogenic, neurogenic, or metabolic in nature, and complete recovery of the patient under treatment usually occurs. It is essential that we take greater interest in these reversible cardiac disturbances instead of continuing to be interested mainly in organic heart disease, from which complete recovery is rare.

3 Some of the etiologic factors, particularly those which are psychogenic, neurogenic, metabolic, and infectious in character, can be superimposed on the common organic diseases of the heart, and they accentuate the cardiac damage. The correct clinical appraisal of a cardiac patient often necessitates not only a complete qualitative analytical separation, but also a quantitative estimation of each active etiologic factor.

4 Application of the considerations here discussed is of

practical significance, not only in internal medicine, but also in surgery and in the specialities

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## DETAILED NON-SURGICAL TREATMENT OF BRONCHIECTASIS

### CLASSIFICATION OF BRONCHIECTASIS

THERE are two main types of bronchiectasis. In the first type the disease starts in childhood after some form of acute respiratory infection. In only rare cases is there proof that the bronchiectasis itself is congenital or is associated with congenital atelectasis or cystic disease. The second type starts at a later age and is the result of bronchial obstruction by foreign body, benign or malignant tumor, tuberculosis, or other chronic inflammation. Between these two clear-cut types of the disease there are varying degrees of bronchiectasis which have their onset at any age from a variety of known or unknown causes. In this paper we shall pay most attention to the first type.

### PROGNOSIS

Bronchiectasis may involve only part of one lobe, the whole of one lobe, or part or all of many lobes, but after it is once established it seldom spreads from one lobe to another. This is an important point in prognosis and one that is not usually recognized. However, the infection in the bronchial walls may progress and involve the peribronchial and pulmonary tissues. When this happens there is true bronchopulmonary suppuration amounting to multiple pulmonary abscesses with foul sputum. In a surprising number of cases, however, the pathologic process does not extend beyond the peribronchial tissues.

People with bronchiectasis may live for many years, but there is a strong clinical impression that those who develop

the disease before they are ten years old seldom live beyond the age of forty. To obtain statistics on the prognosis in bronchiectasis Dr. Kenneth Perry has recently reviewed 404 cases treated at the Massachusetts General Hospital in the past twelve years. Two hundred and sixty patients had only medical treatment, and sixty-six, or 25 per cent, of these are already dead. Thirty-five died of pneumonia, nine of right-sided heart failure, eight of brain abscess, four of massive hemorrhage, and only five of conditions not directly associated with the bronchiectasis. Ninety-four of the non-surgical cases developed symptoms of their disease before the age of ten and twenty-one of these have died. Thirty-three had their symptoms for more than twenty years and eight have died. It is of interest that of the total 404 patients, 45 per cent had symptoms before the tenth year of age and only nine patients over forty years dated the onset to childhood. These are only preliminary figures, but they support the clinical impression of the high mortality of the disease.

As might be expected, the saccular and cystic forms of the disease have a higher mortality than the cylindrical, and the bilateral basal processes more than the unilobar.

#### STUDY OF THE INDIVIDUAL CASE

Careful diagnostic study is the first step in the treatment of any case of bronchiectasis. This involves the following procedures:

1. Ordinary roentgenograms should be taken in both the postero-anterior and lateral positions. The postero-anterior film may show compensatory emphysema in the left upper lobe, but the collapsed lower lobe concealed behind the heart may appear only in a lateral film. The lateral film is essential also to prove disease in the right middle lobe or in the lingula of the left upper lobe.

2. Careful lipiodol studies should be made to show the location and extent of the bronchiectatic lesions. All patients should have postural drainage before lipiodol is instilled, otherwise a complete bronchogram will not be obtained.

3. Bronchoscopic examination is important if there is any evidence of bronchial obstruction from foreign body, benign or malignant tumor, or acute, subacute or chronic inflammatory tissue. If the obstruction can be safely removed at the time

of bronchoscopy, decrease in cough, sputum and fever will result.

4 There is much doubt as to the etiologic relationship between sinus infection and bronchiectasis, but sinus disease so commonly accompanies bronchiectasis that the sinuses should be studied in each case and treatment instituted if necessary. The cooperation of an otolaryngologist of sound judgment is essential.

5 Bacteriologic examination of the sputum should be made, although it is very difficult to find the true etiologic organism in any large percentage of cases. If the fusospirochaetal group of anaerobic mouth organisms is present in large numbers, arsphenamine treatment may be helpful. Likewise, specific measures may be instituted for hemolytic streptococcus infection. Drug treatment will be considered in more detail later.

6 The etiologic significance of allergy in bronchiectasis has recently been emphasized. It is doubtful that an allergic factor will be discovered in many cases, but it should be sought. If present, reasonable treatment should be started. Certainly small areas of atelectasis occur in association with asthma, and it is possible though unlikely that bronchiectasis develops in these areas.

7 The patient's general condition is of great importance in determining treatment, and careful study may show anemia, right-sided heart failure, or amyloid disease.

#### SURGICAL TREATMENT

The purpose of this paper is not to discuss the surgical treatment of bronchiectasis but to review the non-surgical measures which have been shown to relieve the symptoms. Medical treatment, however, offers no hope of cure and, at best, only partial relief. On the other hand, in 127 carefully selected cases at the Massachusetts General Hospital in which the modern type of lobectomy has been performed, forty-eight of the patients consider themselves cured and forty-three more report 85 to 95 per cent relief. The operative mortality is only 3.4 per cent.

Therefore, the possibility of surgical removal of the diseased areas is the first thing to consider. If surgery is contraindicated or postponed, we must be satisfied with medical

measures These measures may be grouped under three headings (1) those that are definitely beneficial, (2) those that are worth trying, although the results are not certain, and (3) those that have been suggested in the past but are not worth using except for special indications

#### MEDICAL MEASURES OF PROVED VALUE

**Postural Drainage**—This is one measure of almost certain value in all cases of bronchiectasis. Remarkable improvement follows its establishment. The temperature drops, there is a gain in weight, cough and expectoration are definitely decreased and the sputum becomes less foul. The frequency and length of the drainage periods depend upon the age and general condition of the patient. A hot drink before drainage is often helpful in starting expectoration.

In suppurative conditions of the lung the position to be assumed depends ordinarily upon the location of the diseased process. The lower lobes are usually involved in bronchiectasis and drainage is best promoted by the patient's lying on his face with the shoulders below the level of the hips. Most patients prefer to lie across the bed with the shoulders near the floor, but some kneel in a chair with the hands on the floor. If a postural drainage table is available, the body can be tilted at an acute angle, but this position cannot be maintained for more than a few minutes. Nelson<sup>1</sup> has designed a postural drainage bed, the center of which can be made to rise by winding a handle. The patient lying on his face with his hips at the peak is more comfortable than on the ordinary drainage table where his feet are elevated. In certain cases the drainage position is assumed for a few minutes several times a day. Occasionally constant drainage is indicated and the patient can lie face down with the foot of the bed elevated.

If the bronchiectasis is in the right middle lobe or the lingula of the left upper lobe, the best drainage is obtained with the patient lying on his back and the foot of the bed moderately elevated. In the rare upper lobe cases the sitting position is usually most satisfactory. If the disease is in the lower part of the upper lobe, the position of choice is lying on the uninfected side.

In all cases the important thing is to find the position which

gives the best results regardless of the anatomic location of the lesions

**Bronchoscopic Drainage.**—Postural drainage is not always sufficient. Fever and foul sputum may persist and bronchoscopic drainage may be necessary. A single treatment may remove the foul secretion, or a series of treatments at weekly intervals may be required. Bronchial lavage with salt solution or the introduction of gomenolized oil or lipiodol are occasionally beneficial. Bronchoscopic drainage seems a drastic procedure, but patients who receive it are often aided enough to insist on its continuation.

**General Medical Treatment**—General medical treatment is of particular importance in children or in patients being prepared for operation. Carefully supervised postural drainage, regular periods of rest, treatment of anemia and a well-balanced diet show surprising results. The diet must have sufficient caloric, adequate protein and high vitamin content. Heliotherapy may be added to this general program but is not in itself of great importance. Such a program is often best maintained in an institution.

#### MEASURES OF POSSIBLE VALUE

**Drugs**—Drugs are used to increase expectoration, to act as bactericidal agents, and to overcome foul odor. Potassium iodide is the best expectorant, but its action is not striking in these cases. Two drugs are used for their bactericidal effect: neoarsphenamine if fusospirochaetal organisms are found in abundance, and sulfanilamide in the rare case with a predominant growth of hemolytic streptococci. The dose of arsphenamine should be about two-thirds the dose used in treating syphilis. Treatment should be given twice a week and six doses usually suffice. Arsphenamine also helps in overcoming the foul odor of the sputum. Creosote and gomenol have a similar action. Creosote may be given by mouth or in an enema of three or four drops of birch creosote added to three or four tablespoonfuls of tepid milk. There has recently been placed on the market a preparation (Guajakodyl) that can be injected hypodermically. Gomenol is best administered in capsules or perles.

**Lipiodol Injections**—Lipiodol is used in the therapy as well as in the diagnosis of bronchiectasis. Opinions as to its



action vary. Some say that it dilutes the sputum and allows it to be raised with less difficulty, others that it prevents irritation by coating the bronchial walls, and still others that it is heavier than sputum and sinks to the bottom of the bronchiectatic cavities, displacing secretions otherwise hard to raise.

The customary procedure is to give four or six injections of 10 to 20 c c at weekly intervals. The oil may be introduced through the bronchoscope, as mentioned above, or by the simpler methods of Singer,<sup>2</sup> Pritchard,<sup>3</sup> or Ochsner.<sup>4</sup> Singer uses little or no local anesthesia. The syringe is provided with a straight cannula. The tongue is pulled forward as far as possible, the cannula placed at the level of the uvula, and the patient instructed to take deep breaths and not to cough. The oil is then injected into the inter-arytenoid fossae and trickles between the vocal cords during phases of respiration. Pritchard uses local anesthesia and injects the oil into the hypopharynx or between the vocal cords through a curved cannula. Ochsner starts with an antiseptic mouth wash, uses local anesthesia, has the patient inhale novocaine solution (which has been placed in the mouth) and then inhale the lipiodol solution from the mouth. These methods are described in detail in the articles mentioned in the bibliography.

**Climate**—There is no doubt that the majority of patients with bronchiectasis are better in the summer than in the winter, and it would naturally follow that they are better in high, dry climates than in localities with changeable and humid atmospheric conditions. Climate does not, however, cure the disease.

**Roentgen Therapy**.—A few years ago good results of x-ray treatment of bronchiectasis were reported.<sup>5</sup> Since then many observers have experimented with small series of cases without striking results and the method has not found particular favor. In obstinate cases it is worth a trial.

#### MEASURES OF LITTLE VALUE

**Abdominal Belt**—If emphysema complicates bronchiectasis, a special abdominal belt which pushes the diaphragm upward may relieve the dyspnea. To be effective such belts must be made to order from careful measurements of the patient. Alexander<sup>6</sup> and Gordon<sup>7</sup> have described proper abdominal supports.

**Inhalation.**—Inhalations of medicated steam have proved of little value, but creosote vapor baths give temporary relief from foul sputum. Punch and Knott<sup>8</sup> give the following description of the method. "A special air-tight room is essential, hence the treatment is usually only feasible in an institution. The creosote is vapourised in a flat metal dish placed on a tripod over a spirit lamp. The patient sits on a chair placed some distance from the tripod, his clothes being protected by an overall, the nostrils plugged by cotton wool and the eyes protected by goggles. When the lamp is lighted the room is filled with dense fumes, which cause the patient to cough violently and expectorate profusely. The baths are given two to three times daily, starting with ten minutes' exposure to the fumes and increasing gradually up to half an hour. There is a certain amount of discomfort associated with the treatment at first, but the patients soon get used to it and the relief they experience fully compensates for the inconvenience. Here again the treatment is purely palliative and the condition is likely to relapse when it is discontinued."

**Artificial Pneumothorax.**—This procedure is recommended by Rist,<sup>9</sup> but in recent years lobectomy has taken the place of compression therapy.

#### TREATMENT OF COMPLICATIONS

The two most common complications are pneumonia and hemorrhage. Pneumonia should be treated as if bronchiectasis were not present, but it may be very difficult to isolate the etiologic organism from the sputum. Serum and sulfapyridine must be used with caution.

There is no satisfactory treatment for pulmonary hemorrhage. Rest usually suffices. Ten cubic centimeters of a specially prepared 1 per cent solution of Congo red may be given intravenously. Artificial pneumothorax is rarely of help in stopping bleeding from bronchiectatic cavities, though its use is justified when there is profuse hemorrhage. Temporary paralysis of the phrenic nerve may have some good effect. Transfusion is sometimes necessary to save life.

#### PREVENTION

There is much speculation as to the conditions necessary for the development of bronchiectasis. Many investigators be-

lieve that some degree of bronchial obstruction or atelectasis is needed to produce bronchial dilatation. They do not believe that simple infection in the bronchial mucous membrane will lead to bronchial dilatation. It seems especially important in the pneumonias of children to watch for atelectatic areas and be sure that they have cleared before the patient is discharged from the physician's care. Of equal importance is the follow-up in cases of postoperative atelectasis, although in a large series of cases there are very few instances of bronchiectasis having followed operations other than tonsillectomy.

Once the condition is established, its exacerbations can be prevented by the best of hygienic care, the avoidance of fatigue and acute respiratory infection, and conscientious attention to postural drainage.

### SUMMARY

Ordinary bronchiectasis is a disease starting in childhood and remaining localized in the lobe or lobes originally involved. However, the infection may spread beyond the bronchial walls and involve the pulmonary tissues. The mortality is high (25 per cent in a series of 260 non-surgical cases observed for twelve years) and there is statistical evidence to show that few patients live for more than thirty years. Death can usually be ascribed directly to the pulmonary disease.

Lobectomy is the treatment of choice, but when it cannot be used the following measures should be employed: postural drainage, bronchoscopic drainage, general medical care, expectorants, drugs to minimize the foul odor, and a number of other measures when there are special indications.

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### EMPHYEMA THORACIS. AN ANALYTICAL STUDY OF 500 CASES WITH GENERAL REMARKS\*

THE recent development in bacteriologic classification and in the serum and chemotherapeutic treatment of pneumonia invites an appraisal of these factors in regard to its most common complication. The relationship of these factors to pneumonia has been thoroughly investigated by Finland and his coworkers† at the Boston City Hospital. In reviewing this and additional material from the same hospital from the point of view of empyema thoracis, the writer has collected 500 consecutive cases of the condition (chiefly acute) occurring in children and adults over a period of seven years, from 1932 to 1939. In this series are also included postmortem cases in which empyema was discovered either as a major or minor condition.

**Incidence of Empyema**—From Finland's<sup>2</sup> series of 3,131 cases of pneumococcic pneumonia it may be computed that empyema occurred in 11.7 per cent. In his series<sup>4</sup> of 684 autopsied cases of pneumococcic pneumonia this condition occurred in 18.1 per cent. In this series the incidence of Type I empyema in 547 cases of Type I pneumonia was 10.2 per cent.

**Age** (see Table 1)—In the present series of 500 cases, empyema occurred most frequently in the first ten years of life (162 cases, 32.4 per cent). The next most frequent group

\* Assistance in the preparation of this material was furnished by the personnel of the Works Progress Administration, Official Project, No. 17580.

† References 1 to 7, inclusive, in bibliography. To be consulted for details relative to selection of cases, treatment, etc., during the pneumonic stage.

Type I *Pneumococcus* was found in the blood stream in forty-two cases, or 44.6 per cent of the pneumococcus cases. Types II, III, V, VII, VIII, and XVIII followed in order of frequency.

The mortality in ninety-four pneumococcal bacteremic cases was 40.4 per cent. Type III, occurring in nine cases, showed 100 per cent mortality. Type I bacteremia mortality was 35.7 per cent.

*Streptococcus haemolyticus* occurred in sixteen, or 13.3 per cent, of all bacteremic cases. The death rate in these cases was 47 per cent.

*Staphylococcus aureus* was found in the blood stream in four cases, or 3.3 per cent, of all bacteremic cases. The mortality in this group was 75 per cent.

In the miscellaneous group there was one *Streptococcus haemolyticus*-*Staphylococcus aureus* infection, four Friedlander bacillus infections, and one *Staphylococcus aureus* infection.

The gross mortality in 101 *non-bacteremic* cases was 36.6 per cent. In thirty-eight *non-bacteremic* *Pneumococcus* empyema cases the mortality was 39.5 per cent. The mortality in twenty-nine *non-bacteremic* *Streptococcus haemolyticus* empyema cases was 53 per cent.

**Serum-treated Cases** (see Table 8) —Specific serum was administered to fifty-five patients during the pneumonia stage.

TABLE 8

ANALYSIS OF 55 EMPYEMA CASES TREATED WITH SPECIFIC SERUM

Serum type	Cases treated before 5th day of pneumonia		Cases treated after 5th day of pneumonia		All serum treated cases	
	Number of cases	Mortality per cent	Number of cases	Mortality per cent	Number of cases	Mortality per cent
I	26	19.2	12	41.6	38	26.3
II	6	50.0	4	25.0	10	40.0
V	3	33.3	1	0	4	25.0
VII	1	100.0	0	0	1	100.0
VIII	1	100.0	1	100.0	2	100.0
Total	37	28.6	18	38.8	55	32.7

Thirty-seven of these recipients of serum were treated before the fifth day of their pneumonia, showing a mortality of 28.6 per cent. Eighteen treated after the fifth day of the pneumonia

showed a mortality of 38.8 per cent. The gross mortality for all serum-treated pneumococcus cases was 32.7 per cent. The death rate for 237 patients with pneumococcal empyemas receiving neither serum nor sulfanilamide was 38.4 per cent.

Type I serum was given to thirty-eight patients, twenty-six receiving the antibody before and twelve after the fifth day of pneumonia. The death rate in these twenty-six cases was 19.2 per cent as compared with 41.6 per cent for the twelve treated later. The mortality rate in all Type I serum-treated cases was 26.3 per cent. In ninety cases of Type I empyema receiving neither serum nor sulfanilamide the mortality was 10 per cent. Several factors account for this paradoxical fact, among which is the observation that 83.6 per cent of the serum-treated cases showed bacteremia, whereas only 40 per cent of the non-serum-treated cases showed positive blood cultures.

*The Effect of Serum Treatment on the Incidence of Emphyema*—This was studied in Type I adult patients over a five-year period from 1933 to 1938 (see Table 9). During this

TABLE 9

INCIDENCE WITH RESPECT TO TYPE I PNEUMONIA OF 56 CASES OF ADULT TYPE I PNEUMOCOCCIC EMPHYEMA

	Type I adult pneumonia. Number of cases	Type I adult empyema. Number of cases	Incidence, per cent.	Serum treated per cent Pneumonia.	Mortality, per cent	
					Pneumonia.*	Empyema.
1933-1934	97	9	9.3	57.0	33.0	55.0
1934-1935	114	8	7.0	59.6	34.1	37.0
1935-1936	129	16	12.4	53.0	31.0	19.0
1936-1937	102	11	10.8	77.0	26.4	36.0
1937-1938	105	12	11.4	89.0	20.0	17.0
Total	547*	56	10.2			

\* Adult, Type I pneumonia patients serum and non-serum-treated.

period 547 patients with Type I pneumonia showed a slightly increasing annual occurrence from ninety-seven to 105 cases. In spite of an increase in serum therapy from 57 per cent to 89 per cent, the incidence of Type I pneumococcus empyema showed a slight increase from 9 to 12 per cent, with a peak of 16 per cent in the middle year of this period (1935-1936).

*Serum Treatment and Blood Culture*—Of the fifty-six serum-treated patients, forty-six (83.6 per cent) showed posi-



tive blood cultures There was practically no difference in the mortality in the bacteremic and non-bacteremic serum-treated cases, which showed 32.6 and 33.3 per cent, respectively

In the Type I serum-treated group, however, there were no deaths in four non-bacteremic cases, whereas ten deaths (29.4 per cent) occurred in thirty-four bacteremic cases In twenty-two bacteremic cases, treated before the fifth day of pneumonia, the mortality was 19.2 per cent as compared with 41.6 per cent in the twelve cases in which treatment was later

**Sulfanilamide Treatment**—Fourteen patients with pneumococcal empyema (9 adults, 5 children) received an average daily dose of 2.9 gm of sulfanilamide during pneumonia Six of these patients died (43 per cent mortality) None of these patients received specific serum

Twenty-four patients with hemolytic streptococcal empyema (21 adults, 3 children) received an average of 3.4 gm of sulfanilamide daily Seven of these patients died (29 per cent mortality) This death rate was distinctly lower than that of 48 per cent observed in the cases of *Streptococcus haemolyticus* infection which did not receive this drug

There were no deaths among four adult patients with sterile empyema, two of these showed *Streptococcus haemolyticus* in the sputum and received an average daily dose of 3.6 gm of sulfanilamide

Two patients with a *Staphylococcus aureus* infection (1 adult, 1 child) received a daily dose of 6 and 1 gm, respectively, of sulfanilamide The adult died

**Sulfapyridine Therapy**.—This drug was employed in two cases of empyema, in both of which the patients recovered The first patient was a sixty-one-year-old man with a Type I pneumonia who received both sulfapyridine and Type I serum on the third day of the disease, with a prompt fall in temperature but subsequent rise to 103° F on the sixth day of pneumonia Thoracentesis on the twentieth hospital day yielded 75 c c of thick Type I pus Three days later the temperature dropped to normal under continued sulfapyridine treatment This patient was discharged on the thirty-sixth day after the onset of the pneumonia

The second patient, a nineteen-year-old male with a Type V infection, was started on sulfapyridine treatment on the eighth day after the onset of pneumonia when he showed signs of

massive effusion Six aspirations, yielding progressively diminishing amounts from 1,000 c.c. to 250 c.c., were carried out Rib resection, delayed on account of extreme toxicity until the twenty-first day of the disease, was necessitated by the viscosity of the effusion The cavity measured 350 c.c. at operation The temperature, which ranged between 99.5° and 103° F, dropped to normal on the first day after operation and the patient was discharged on the eleventh postoperative day with a cavity measuring 60 c.c. The average dosage of sulfapyridine was 4 gm. per day over a period of nineteen days

**Various Forms of Drainage** (see Table 10) —In 502 cases of empyema, 102 were not drained because of the pa-

TABLE 10

RESULTS OF VARIOUS FORMS OF DRAINAGE IN 502\* CASES OF EMPYEMA

	Total	Lived.	Died.	Mortality per cent
No drainage†	102	2	100	98.0
Thoracentesis—single or multiple	100	42	58	58.0
Closed drainage (intercostal thoracotomy)	94	69	25	26.6
Closed drainage followed by open drainage	33	27	6	18.2
Open drainage (rib resection)	159	142	17	10.7
Secondary rib resections or partial thoracoplasties	14	12	2	14.3
Total.	502	294	208	41.4

\* 500 cases, 2 readmissions (159 acute cases) This table includes all cases whether or not patients received specific serum or sulfanilamide.

† Patients chiefly moribund. Rare unsuspected empyema coming to autopsy Eleven patients received serum four were treated with sulfanilamide.

‡ Not followed by other forms of drainage.

tients' moribund condition or the incidental nature of the empyema The gravity of the condition is indicated by the mortality of 98.0 per cent in this group

Single or multiple aspiration without subsequent operative drainage was carried out in 100 cases with a mortality of 58.0 per cent This high mortality also attests the serious condition of these patients

Closed drainage (intercostal thoracotomy) was carried out in ninety-four cases, resulting in a mortality of 26.6 per cent

Open drainage (rib resection) was carried out in 159 cases with a mortality of 10.7 per cent

Closed drainage followed by open drainage (thirty-three cases) showed a mortality of 18.2 per cent

Secondary rib resections and partial thoracoplasties were done in fourteen cases with a mortality of 14.3 per cent

**Autopsy Data**—Postmortem examination was performed in 118 cases. The *empyema cavity* was found on the right side in 48.2 per cent, on the left side in 37.7 per cent, bilaterally in 14.1 per cent. The most frequently occurring size at autopsy was between 100 to 200 c c and this occurred in 21.5 per cent. Next in order were cavities of 1,000 to 2,000 c c (15.2 per cent), 500 to 600 c c (13.5 per cent), and 400 to 500 c c (11.5 per cent).

*Postmortem bacteriologic examination* showed pneumococci in eighty-seven empyema cultures (50.5 per cent). *Streptococcus haemolyticus* was found in thirty-one cultures (18.3 per cent), *Staphylococcus aureus* in thirteen (7.7 per cent), *Bacillus coli* in eleven (6.6 per cent), etc. Of the eighty-seven pneumococcus cultures, Type III predominated with fourteen instances (16.1 per cent). Closely grouped were

TABLE 11

COMPLICATING OR ASSOCIATED FOCAL INFECTIONS OBSERVED IN 118 AUTOPSED CASES OF EMPYEMA

Focal infection	Number of cases	Incidence, per cent.
Pericarditis	20	16.9
Otitis media	8	6.7
Vegetative endocarditis	7	5.9
Peritonitis	6	5.1
Meningitis	4	3.3
Central necrosis of liver	3	2.5
Acute nephritis	2	1.7
Abscess	2	1.7
Pectoral (empyema necessitatis)	2	1.7
Subdiaphragmatic (causing empyema)	1	0.8
Total	53	

Types VI (12.6 per cent), VII (12.6 per cent), I (11.5 per cent), V (11.5 per cent), and VIII (10.3 per cent).

*Pulmonary pathology* revealed lobar pneumonia in fifty-four (45.6 per cent) instances, bronchopneumonia in fifty-three (45.0 per cent), gross single or multiple abscesses in nineteen (16.1 per cent), pulmonary tuberculosis in seven (5.9 per cent), pulmonary malignancy in three (2.5 per cent), pulmonary artery thrombosis in two (1.7 per cent), anthracosis in one (0.8 per cent), septic pulmonary infarcts in one (0.8

per cent), pulmonary arteriosclerosis in one (0.8 per cent), and pulmonary emboli in one (0.8 per cent)

*Cardiovascular disease* occurred in thirty-eight cases (32.2 per cent), arteriosclerosis in eighteen (15.2 per cent), coronary disease in eleven (9.3 per cent), hypertensive heart disease in seven (5.9 per cent), and rheumatic heart disease in five (4.2 per cent)

*Complicating or associated focal infections* occurred in fifty-three cases (see Table 11). The most common of these conditions was suppurative and fibrinous pericarditis which was found in twenty cases (16.9 per cent). Otitis media, vegetative endocarditis, peritonitis, meningitis, central necrosis of the liver, acute nephritis and pectoral abscess followed in order of frequency.

#### GENERAL COMMENT

The analysis of this group of 500 cases together with personal observation of a large portion of this series permits of several generalizations concerning empyema thoracis.

Delay in diagnosis is understandable in cases which prove to have small collections of pus (50–100 c.c.) between the lower lobe of the lung and the diaphragm, between the mediastinal surface of the lung and the pericardium, or in interlobar fissures. It should be stressed, however, that free effusions, often as large as 1,000 c.c. are unrecognized from time to time. *Frequently, x-ray films appear to be negative during the early stage of empyema.*

On the basis of an average incidence of 24.3 per cent of empyema in Type I pneumonia and 11 to 18 per cent in all pneumococcal pneumonias, *one should strongly suspect empyema if fever persists after the normal course of seven to ten days of the disease. Search for typical or atypical localization should be carried out and thoracentesis should be performed by the twelfth to the fifteenth day after the onset of pneumonia.*

Although pneumococcus empyema is usually a *post-pneumonic* manifestation, it should be borne in mind that it may rarely occur as a *synpneumonic* complication. A case in point is that of a forty-three-year-old man who died on the fifth day of pneumonia with a 400 c.c. Type I purulent effusion.

The high incidence of empyema in children is another fact

which should encourage diligent search for the condition in childhood. Physical signs are vastly more efficient weapons to use and are extremely reliable in the hands of good practitioners.

The preponderance of the disease in males (23:1) is also a valuable diagnostic aid.

The bacteriologic analysis in this series indicates that 63 per cent of all empyemas are due to the *Pneumococcus*. The nearest approach to this frequency is the 15 per cent incidence due to *Streptococcus haemolyticus*. *It is obvious, therefore, that every pneumococcal pneumonia should be regarded as a potential empyema. This is especially true if pneumococcal bacteremia is present before specific therapy is started, as demonstrated by Finland*<sup>3, 5</sup>

In several cases it has been observed that Type I pneumococcal bacteremia merges into pure *Streptococcus haemolyticus*, with subsequent development of empyema containing the latter organism. *This shift in the bacteriology of the blood stream has in our experience been a bad omen.*

*Specific Type I serum therapy* has (1) reduced the incidence of empyema in non-bacteremic Type I pneumonia to 0.8 per cent (Finland<sup>1</sup>), (2) it has reduced the Type I empyema mortality from 55 per cent in 1933-1934 to 17 per cent in 1937-1938, (3) it has reduced the Type I empyema mortality to 19 per cent in twenty-six cases receiving the antibody before the fifth day of pneumonia as compared to 41 per cent mortality in twelve cases treated after the fifth day. But serum therapy has not reduced the incidence of Type I empyema.

*Sulfanilamide therapy* reduced the *Streptococcus haemolyticus* empyema mortality from 48 per cent in fifty-one untreated cases to 29 per cent in twenty-four treated cases.

*Early recognition of empyema necessitates early drainage of the proper sort without delay.* Empyema may be cured by thoracentesis alone, in fact, five or six patients with cavities of 50 c.c. or less were cured by a single aspiration. In most instances three aspirations were carried out in cases cured by this procedure. *The cases amenable to thoracentesis alone rarely show more than 100 c.c. of fluid.* It follows, therefore, that multiple aspirations, averaging 400 to 500 c.c. in a post-pneumonic empyema, represent a misconception of the

limitations of this procedure Nature, however, frequently steps in by producing pus which is impossible to aspirate with even large needles

Therapeutic aspiration has its place in very sick patients, particularly cases of *Streptococcus haemolyticus* empyema In these cases we have found, however, a more lasting reduction in temperature when closed intercostal thoracotomy was carried out after the third to the fifth thoracentesis This procedure was often, but not necessarily, followed by rib resection Most cases of *Streptococcus haemolyticus* empyema should be considered from the point of view of rib resection two weeks after closed thoracotomy if accompanied by continued fever of  $103^{\circ}$  to  $104^{\circ}$  F, provided that the fever is, of course, not due to such complications of pneumonia as pericarditis, endocarditis, otitis media, meningitis, etc Rib resection should be practically imperative if drainage is unsatisfactory following intercostal thoracotomy, as evidenced by persistence of fluid by physical signs or x-ray examination The continuation of intercostal drainage for five to six weeks in the presence of fever and continued signs of fluid is hardly excusable regardless of the bacteriology

A glance at the mortality associated with various forms of drainage at once reveals the fact that rib resection (open drainage), with a death rate of 10.7 per cent, carries the lowest mortality in a general hospital not equipped for special drainage technics *Rib resection is therefore the form of treatment to aim at* unless the usual contraindications of severe toxicity, lack of fixation of the mediastinum, extreme age limits, etc, are present It is the writer's contention that practically every adult developing pneumococcic empyema can and should have rib resection within five to ten days after the first demonstration of organism-containing effusion Waiting for pus to "thicken up" is usually overdone It adds unnecessary days of convalescence

The writer feels that practically all pneumococcic pneumonias have sufficient fibrinous pleural reaction around the mediastinum by the time empyema develops so that open drainage may be carried out in the presence of moderately thin pus without danger of mediastinal "flutter" The writer has performed rib resection on the twelfth day after the onset of Type I pneumonia, the first positive chest tap having been

obtained on the ninth day. In spite of quite thin pus, open drainage caused no respiratory embarrassment with slow decompression at the time of operation.

*Ideally, therefore, a post-pneumonic empyema should be recognized by the tenth to the fifteenth day after the onset of pneumonia and rib resection or closed drainage should be carried out by the twentieth day except in rare instances which yield to several chest taps.* Infants do well with closed drainage even in pneumococcic empyema, but they may require rib resection later. Children over four years of age can tolerate primary rib resection in pneumococcic empyema.

The average hospital stay after either rib resection or closed drainage was forty-one days.\* These patients were discharged completely healed. Cases that are unhealed by three months have been arbitrarily labeled "chronic empyemas" in most clinics and with justification.

The most serious type of empyema from the bacteriologic viewpoint is that due to putrefying organisms, the so-called "*putrid*" empyema. This kind of empyema is secondary usually to perforation of a lung abscess, bronchiectatic abscesses, or abscess associated with carcinoma of the lung. The patient with this disease is not only depleted by the chronic pulmonary infection or malignancy, but is burdened by an effusion which has a *special predilection for producing an overwhelming anaerobic cellulitis of the chest wall, even after one thoracentesis* in some instances. *Such cases should not be subjected to repeated thoracentesis nor to closed drainage for this reason.* Open drainage, with or without closed pleurotomy, is the only safe method of attacking these cases. Anaerobic cellulitis of the chest wall is thus avoided by an open wound of the chest wall, while respiratory distress may be controlled if necessary by inserting a tightly fitting rubber tube into the pleura which will remain air tight for a sufficiently long time.

Chronic empyema usually results from an inadequately drained acute empyema, the presence of a foreign body (rubber drain), osteomyelitis of the rib, persistent bronchial fistula, etc. Occasionally a slowly growing malignancy is found to be the underlying cause. Benign dermoid cysts or teratomata may break down to simulate encapsulated empyema. Tuber-

\* In sixty-three cases on the service of the writer.

culosis and parasitic diseases should, of course, be kept in mind as possibilities. Biopsy of a chronic draining sinus may yield information where bacteriologic studies are fruitless. Tuberculous empyema uncomplicated by purulent infection should be treated by repeated thoracentesis. Purulent invasion usually calls for rib resection.

Such supplementary therapeutic procedures as transfusion (particularly in *Streptococcus haemolyticus* infections), treatment of the anemia which frequently appears in these patients, adequate dietary and vitamin intake, and ultraviolet treatment, are as important to bear in mind in these cases as the specific forms of therapy.

The frequency with which patients with empyema show other complications of pneumonia or are afflicted with other systemic conditions is illustrated in the autopsy data. It is the conviction of all clinicians interested in empyema that these additional complications are the overwhelming cause of death in empyema. Alertness in this direction is one of the keynotes to improvement of the treatment of empyema patients.

### *Acknowledgment*

The writer wishes to acknowledge his gratitude to Dr Maxwell Finland for allowing him to use his data and for his helpful suggestions.

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### DIAGNOSTIC PROBLEMS OF TUBERCULOSIS

MORE than fifty years ago Doctor Edward Livingston Trudeau said to a group of his students that if a patient came to them with a dry pleurisy, blood-spitting, or a cold abscess it was wise to consider him as tuberculous and to treat him as such until the contrary could be proved

Today, our armamentarium for making the early diagnosis of tuberculosis is adequate Our knowledge of the use of these facilities, however, does not appear to keep pace with their development Only 13 per cent<sup>1</sup> of all sanatorium admissions in this country are in the minimal stage of the disease In other words, 82 to 87 per cent of all pulmonary tuberculosis goes undiagnosed until it reaches advanced disease We will be largely concerned in this clinic with the diagnostic problem of minimal tuberculosis

#### DIAGNOSIS OF TUBERCULOUS DISEASE IN ITS EARLY AND MINIMAL FORM

What do we mean by "minimal" tuberculosis? The National Tuberculosis Association has defined it as follows<sup>2</sup> "A slight lesion without demonstrable excavation confined to a small part of one or both lungs The total extent of the lesions, regardless of distribution, shall not exceed the equivalent of the volume of lung tissue which lies above the second chondrosternal junction and the spine of the fourth or body of the fifth thoracic vertebra on one side"

This classification is, of course, based on the anatomical extent of the disease in the lung But smaller lesions of 1 to 3 cm are often seen by x-ray examination. An evaluation of

the age and character of these lesions is important. Pulmonary tuberculous infection begins in the lung as a microscopic tubercle and cannot be diagnosed until it progresses to sufficient size to give constitutional symptoms of disease, or to cast a shadow by x-ray, or caseate into a bronchus, producing tubercle bacilli in the sputum. This early lesion, however small when first discovered, is potentially advanced disease. It may retrogress and leave behind but a small scar. It may lie latent for months to years and then spread. Or it may quickly caseate and spread into a destructive process. The lasting cure of this early lesion has been well discussed by Amberson.<sup>3</sup>

The earliest possible diagnosis of tuberculosis comes by mass examination methods. This routine use of tuberculin and x-ray may reveal many healed and innocent lesions along with active disease.

These surveys have shown us the dangers of infection in early adult life. They have taught us to discriminate between tuberculous infection as shown by the tuberculin test, and tuberculous disease as shown by the clinical and x-ray observation of the patient. They have shown a high incidence of infection and disease among those associated with the tuberculous sick.<sup>4</sup> And they have shown that those negative to tuberculin are in greater danger of developing tuberculous disease from exposure to open cases than are those who are tuberculin positive.<sup>5</sup>

But how is the practicing physician to handle this matter of early diagnosis in the most effective and practical way? How may our knowledge of the disease and the facilities for early diagnosis be used to their greatest advantage?

**Clinical Contributions to Early Diagnosis**—If the development of well-marked symptoms of tuberculosis is awaited before diagnosis is made, the disease will have progressed well into the advanced stage. James Maxwell<sup>6</sup> examined 340 tuberculous patients and found the average duration of symptoms to be about a year before the disease was diagnosed. In eighty-five of these there was a previous history of pleurisy, and 219 had significant symptoms for more than three months.

Recent fatigue or weakness or loss of "pep" may be the patient's only complaint. A finicky appetite, vague digestive

symptoms, or slight loss of weight may be revealed. Altered monthly periods in young women are not uncommon. Even transient pleural pain and slight dyspnea should arouse suspicions of tuberculosis.

J. F., a girl of eighteen, had no symptoms of any kind except a slight, fleeting, right-sided pleural pain of three days' duration a week before she was seen. Her physical examination was entirely negative. The tuberculin test was positive. The roentgenogram, however, revealed a small parenchymal infiltration in the periphery of the right mid-lung field with an enlarged hilus gland. This lesion proved to be active and she developed a pleural effusion within five months of its discovery.

A history of hemoptysis, however small, if due to tuberculosis, is a sign of active disease and should never be passed over by the examining physician without x-ray. Wheezing, while usually correctly diagnosed bronchial asthma, may be due to bronchial stenosis from a tuberculous tracheobronchitis.

A careful, painstaking history may be the only aspect of the case which leads one into more minute study and eventually to the diagnosis of early tuberculosis. Each member of the patient's family should be considered for tuberculosis, and especially should we know from what cause other members of the family have died. A college roommate or a business associate may have developed tuberculosis. Occupation may bring exposure to or close association with the disease. Or, as with granite cutters, occupation may predispose to tuberculosis. These facts should arouse suspicion of underlying disease.

A history characteristic of tuberculosis does not always mean disease.

Recently E. L., a girl of twenty-one, reported for examination because of fatigue, loss of "pep," moderate shortness of breath and vague pains in both lungs. Her physical examination was normal except for fever on two occasions (99.0° and 99.4° F). Her pulse rate was slow, and her heart peaceful. It was not felt that she had tuberculosis. However, the family history revealed a sister with pleurisy and effusion and the patient was worried about tuberculosis. x-Ray examination of the lungs was negative. This knowledge that she was free from disease quickly brought an end to her symptoms and her x-ray has remained clear.

Physical examination of the lungs in the case of the very small and early lesion is as a rule negative. At most there may

be a few fine râles at an apex or infraclavicular area or a slight splinting of the affected chest. Complete examination may reveal some loss of weight, a mild anemia, or glands which are unexplained. Fever is likely to be absent in minimal disease, but tachycardia is a more delicate and reliable index of toxicity. The pulse rate, so easily accessible and so often neglected, may lead to a diagnosis of tuberculosis long in advance of the appearance of physical signs in the lungs.

**Laboratory Aspect of Early Diagnosis.**—A positive sputum examination remains always the one unequivocal proof of underlying tuberculosis. But a negative sputum does not exclude tuberculosis in the early lesion, for the early lesion does not produce sputum unless caseation has developed and has brought a discharge of bacilli into a bronchus. Pinner<sup>7</sup> has stressed the wisdom of pursuing the search for bacilli in difficult diagnostic problems by concentration of the sputum, culture, or guinea-pig inoculation. To this may be added gastric lavage of the early morning contents of the stomach. But even these refinements of the simple sputum smear are usually persistently negative in the case of small or early tuberculous lesions.

The tuberculin test wisely used is of importance as a guide in early diagnosis.

R. B., a student nurse of twenty years, was admitted to the hospital because of a dry cough of three weeks' duration, a persistent low-grade fever and dull pain in the left upper portion of the chest. Physical examination revealed fine crepitant râles in the left apex and infraclavicular region. x-Ray examination of the lungs showed a soft mottling which extended from the hilus into the left apex. The process was thought to be tuberculous and the patient was ordered to be held for observation. By some oversight no tuberculin test was done and she was hastily transferred to a tuberculosis sanatorium. Examination on admission there was negative including the roentgenogram of the lungs. The lesion had cleared and her tuberculin test was shown to be negative. The original left apical bronchopneumonia was indistinguishable from tuberculosis by x-ray until the process had resolved.

A positive tuberculin test is, however, indicative only of the presence of tuberculous infection. It tells us nothing of the location or of the anatomical extent of the infection. Neither does it inform us regarding the activity or inactivity of the process. No tuberculin test should be considered negative unless a patient fails to react to 1 mg. of Old Tuber-

culin or its equivalent. A tuberculin test in young, strong adults is usually positive in the presence of tuberculous infection and negative in its absence. A negative tuberculin test, however, is recorded in about 5 per cent\* of those who show definite evidence of hilus calcification. These cases doubtless represent the persistence of calcium at the site of earlier disease which is healed and obsolete.

Complete examination of the blood contributes little or nothing toward establishing a definite diagnosis of tuberculosis. But as part of a complete physical examination, the blood may reveal anemias or dyscrasias responsible for symptoms which may simulate the early clinical history of tuberculosis. An altered sedimentation rate or Schilling count will indicate the presence of infection within the body but give no important help in establishing a specific diagnosis of tuberculosis.

**The x-Ray—Aids and Errors from Its Use in Early Diagnosis**—In the last analysis, it is the x-ray on which we must rely for the earliest diagnosis of tuberculosis, but always in conjunction with a careful history and complete physical examination. In the individual case it is the clinical and x-ray approach which must be made. The x-ray has shown us that the physician must go out of his way in the quest of tuberculosis if he is to make the early diagnosis. Clinical and x-ray examinations of a whole family, where there is one known open case, will reveal in others the earliest beginnings of disease which can be found no other way. Similar examinations of those in close contact with a known open case should be carried out. Large groups, such as nurses and medical students who are frequently in contact with open disease, are best handled by wholesale tuberculin testing, with x-ray examination of all positive reactors. Those showing lesions in the lungs interpreted as tuberculosis should be subjected to the closer scrutiny of clinical and laboratory study, with repeated x-rays.

Roentgenograms interpreted without wide experience have condemned many a patient to an unwarranted invalidism. The smallness of a tuberculous lesion does not ascertain its age. Neither is it possible on a single x-ray observation to be certain whether the small shadow seen is tuberculosis or some

\* From the study of tuberculosis in student nurses at the Boston City Hospital over a five-year period.

other type of infiltration. There is no x-ray lesion characteristic of pulmonary tuberculosis alone. There is no x-ray picture in the development of tuberculosis that cannot be confused with other pulmonary infections such as pneumonia, chronic suppuration, neoplasm, or the pulmonary expressions of cardiovascular disease. Repeated clinical and x-ray observations may be necessary to establish a diagnosis of tuberculosis.

Reliance on x-rays will be directly proportional to the expertness and experience of the interpreter, especially when he is also the clinical observer of the case. The roentgenologist's report, divorced from all clinical knowledge of the case, must be scrutinized if errors in diagnosis are to be prevented. Best of all is a consultation of clinician and roentgenologist, each a special student of his field.

But what of the patient with a negative roentgenogram of the lungs whom we strongly suspect of tuberculosis? There may be a story of hemoptysis, pleurisy, fatigue with slight fever and a rapid pulse, or other symptoms and signs identifiable with tuberculosis. The x-ray examination however is negative. Once again we return to a more careful and thorough search of the history and physical examination to find other causes for the trouble. For further x-ray study, stereoscopic roentgenograms may reveal shadows unseen on a flat plate. x-Ray plates taken in diagonal may bring lesions into view previously hidden by bony structure. Another x-ray examination three to six weeks following a negative roentgenogram may allow enough time for tuberculous disease to develop sufficiently in size to cast an x-ray shadow and be identified.

What of the patient with a negative roentgenogram in the presence of a positive sputum examination? With these individuals we are suspicious of a tuberculous tracheobronchitis or a tuberculous gland that has ruptured into a bronchus. Bronchoscopy should not be delayed in order to solve this problem.

#### THE DETERMINATION OF ACTIVITY IN THE TUBERCULOUS LESION

x-Ray examination of the lungs has made possible such early diagnosis of tuberculosis that it is difficult often to determine whether the small lesion in the lung revealed for the

*first time* is an active tuberculous process or an old and innocent lesion of long standing

The small lesion of 1 to 2 cm is not necessarily an early and active one. Nor is it often possible to tell the nature of the shadow cast by x-ray

R. M., a stenographer of twenty-eight, was admitted to the Thoracic Clinic at the Boston City Hospital because of a loss of about 12 pounds in weight, overwhelming fatigue, and a cough. The history revealed no other aspects of interest and the examination was negative. The x-ray, however, showed a small, irregular area of density in the periphery of the left infra-clavicular area. The patient was transferred for sanatorium care because of the clinical and x-ray findings. She continued to lose weight and ran an irregular 99° F temperature. Sedimentation rates were variable but her pulse was slow. There was no change in the x-ray lesion on repeated examination. Finally she was discharged after three months as an inactive case and, when an extraordinarily complex family problem was straightened out, she gained weight and lost her fatigue. Now, four years later, the appearance of the x-ray lesion is unchanged.

This patient was shown to have an old and innocent x-ray lesion, which in the face of the history and clinical picture had been thought early and active. It is not possible to obtain a precise knowledge of the status of the central portion of the small lesion we see by x-ray nor any knowledge of the patient's own constitutional resistance to the infection except by repeated clinical and x-ray observation.

The x-ray examination by itself is not infallible. Variation in the technic of roentgenography and differences in exposure and penetration of serial plates of the same lesion will so alter the size and appearance of the process that it appears to have changed when in reality it has not. The speed with which a picture is taken will affect the clarity and outline of the shadow seen. Differences in the process of developing, and especially influences of temperature, will affect the character of the final film. Rotation of the chest upon the x-ray film and the position of the x-ray tube in relation to the patient's chest will likewise affect the observed character of tuberculous lesions in a serial study of the roentgenogram. These variations in the character of the lesion are apparent and not real, and they are the cause of grave errors in comparative interpretation.

As in the diagnosis of tuberculous disease, so in repeated



observation of the small *x*-ray lesion there may appear clinical changes indicative of active disease

E D, a twenty-six-year-old laboratory technician, had had a small left infraclavicular lesion under regular observation for more than a year without change in her roentgenogram and without clinical or laboratory signs of activity. Fourteen months after her first examination she reported ahead of schedule because of a small aching pain, at times, beneath the left clavicle, and an unaccustomed fatigue. Physical examination showed nothing new. Her sedimentation rate was a very low normal. There was no fever and the pulse was slow. But *x*-ray examination showed the old lesion nearly doubled in size. Sanatorium treatment brought prompt results and an apparent cure five years later.

Sedimentation rates appear unreliable in their reflection of the character of the minimal tuberculous lesion which presents few or conflicting clinical signs. At the Channing Home for tuberculosis patients in Boston, routine Schilling counts and sedimentation rates have been done regularly on all patients over a six-year period. An analysis of results\* shows that the clinical and *x*-ray study of the patient, along with the sputum examination, has been the most reliable guide to the conduct of the case. Sedimentation rates and Schilling counts have usually reflected the clinical picture, but rarely contributed important information regarding the patient's disease.

#### DIFFERENTIAL DIAGNOSTIC PROBLEMS

If we bear in mind that no clinical picture and no *x*-ray lesion is pathognomonic of pulmonary tuberculosis exclusive of other diseases of the lungs, we shall approach the problem of differential diagnosis with an inquisitive mind. We have stressed the fact that the small *x*-ray lesion of tuberculosis may be an old and innocent process, a latent lesion, or early progressive disease. We shall discuss a few of the diagnostic problems of this type of tuberculosis and touch lightly on differential problems of more advanced disease.

**Acute Respiratory Infections** —One of the most troublesome differential problems is that of acute respiratory infections superimposed on small, old, healed tuberculous lesions revealed by *x*-ray.

\* Unpublished work from the Channing Home

H. K., a married woman of twenty-five, was in the second month of a pregnancy when she developed a troublesome and harassing cough with small sputum that was negative for tubercle bacilli. A fever of 99.0° F hung on and she lost a few pounds in weight. Examination revealed a few transient râles at the left base. At the end of a week of treatment there was very little change in her condition. A roentgenogram of the lungs showed an irregular 2 by 3 cm. lesion in the left infraclavicular region. Going back over the history a story was elicited of repeated hemoptyses seven years before, with fever for two months. Another week of treatment relieved her of the acute respiratory infection. Further x-ray study and clinical and laboratory observation convinced us that this lesion was the scar of a tuberculous infection seven years before. She went safely through her pregnancy and the lesion is unchanged in appearance six years later.

Another problem is lower respiratory infections kept active by upper respiratory disease. Chronic bronchitis with sinusitis or small localized bronchiectasis with draining sinuses may clinically resemble tuberculosis.

Bronchopneumonia and resolving upper lobe pneumonias\* are for a time indistinguishable from tuberculosis by examination and by x-ray when first seen. Tuberculous lobar pneumonia in its early stages may follow closely the course of a pneumococcus pneumonia, only to be diagnosed when clearing of the process does not occur and sputum analysis finally reveals tubercle bacilli.

**Fevers of Long Standing**—Undulant fever, whether due to *B. melitensis* or *B. abortus*, may show a low grade fever for weeks to months with a history and clinical picture often confused with tuberculosis. Transient parenchymal lesions of the lung and hilus adenopathy add confusion to the picture. The diagnosis may be suspected if raw milk is drunk. Specific agglutinations may help to establish the diagnosis definitely.

Tularemia of the typhoidal form, with tularemic pneumonia<sup>5</sup> without local skin lesions or regional or general adenopathy, is distinguished from tuberculosis by specific agglutination. The diagnosis of tularemia in this form is not possible clinically, but may be suspected from a story of tick bites, from the dressing or handling of rabbits, or from laboratory workers associated with the disease.

Streptococcal infections of long standing, subacute bacterial endocarditis, Hodgkin's disease, and hyperthyroidism are conditions of long standing symptomatology often mistaken

\* Refer to case R. B., page 1374

for tuberculosis. These may be difficult to differentiate except by prolonged clinical and laboratory study.

**Cancer of the Lung**—Primary bronchogenic cancer of the lung and metastatic cancer in the early stages of the disease may be difficult to differentiate from the small and early lesion of tuberculosis. The so-called superior pulmonary sulcus tumors originally described by Pancoast<sup>9</sup> present pain in the shoulder and inner side of the forearm, with wasting of the muscles of the hand, together with Horner's syndrome. The x-ray usually shows one or more apical shadows, which with careful study may show erosion of the first or second rib. Doubt has been thrown on this syndrome by Stein<sup>10</sup> who believes that it is an atypical expression of bronchogenic carcinoma arising close to the periphery of the lung apex. Erosion of the cancer through the chest wall with invasion of nearby tissues and nerve structures produces the picture characteristic of this syndrome. In regard to this the following case\* is of interest.

A forty-seven-year-old business man developed an aching pain in the right shoulder shortly after a shooting match five months before admission to the hospital. Four months before admission he developed a slight morning fever which was higher in the evening. x-Rays taken near the onset of symptoms were said to show a "spot" at the right apex. Fatigue became important. Profuse night sweats were frequent. Loss of appetite, loss of "pep" and loss of 30 pounds in weight in five months were noted. The pain grew worse and was aching in character. It was deep in the right shoulder but without radiation down the arm. His father had apparently died of tuberculosis, but his history was otherwise irrelevant.

Examination on admission to the hospital revealed slight splinting of the right upper chest but no other abnormal signs. There was no atrophy of the right hand or arm, nor was there any limitation of motion in the right shoulder girdle. The pupils were equal.

x-Ray examination of the cervical and dorsal spine showed normal bony structure. Stereoscopic examination of the lungs showed a mottled density occupying the right apex, with increased lung markings extending upward from the hilum. The diagnosis of tuberculosis at the right apex was made from the clinical and x-ray studies.

During his forty-three-day hospital stay the patient ran a fever of from 99° to 103° F. x-Rays of the chest, taken toward the end of his stay for bone detail, showed cavities in the area of infiltration in the right apex. He developed a mild anemia, ran a white blood count of 13,000 to 16,000 and lost

\* Case No. 6395 (by permission) from the records of the Clinical Pathological Conferences of the Faulkner Hospital, Jamaica Plain, Mass.

10 more pounds. He produced little or no sputum which, on one examination, was negative. He was finally sent home with a diagnosis of tuberculosis.

Following discharge he continued to run a fever, he lost weight and strength, and died without the appearance of other important signs. At post-mortem examination he was found to have at the right apex a primary bronchogenic carcinoma of poorly differentiated type. There was invasion of the adjacent intercostal muscles and the second and third thoracic vertebrae. The tumor showed extensive necrosis. No tuberculosis was found. At no time was there anything suggestive of Pancoast's syndrome usually described in these apical tumors.

Metastatic cancer of the lung in the early stages of growth presents the story of destructive disease and a roentgenogram which may show small lesions in the upper lung fields like the small early lesions of tuberculosis. Physical examination of the lungs is usually negative, but a complete examination may reveal the primary site of the cancer.

Miliary carcinomatosis of the lung may be indistinguishable from the roentgenogram of miliary tuberculosis or Boeck's sarcoid. The primary lesion may not reveal itself over a period of many months, but bony erosions of the thoracic cage may be seen if carefully searched for.

**Foreign Bodies in the Lung**—Lipoid pneumonias have been called to our attention by Pinkerton<sup>11</sup> and Cannon<sup>12</sup> as a result of the prolonged use of medicated oils as nasal drops and sprays. Debilitated infants account for nearly two-thirds of the cases, but healthy adults show the passage of oils directly to the lungs, especially during sleep. Local inflammatory changes occur in the lungs, from the irritating oils, from cream and cod liver oil aspirated by choking infants as well as from secondary bacterial infection transported to the lungs from acute upper respiratory disease. The clinical picture may be that of bronchopneumonia, but fever may be absent and physical signs few. x-Ray examination shows enlargement of the hilus shadows with parenchymal lesions shading off toward the periphery. This picture may change little from month to month.

Iodized oils for bronchographic study may remain for weeks to years in the interstitial tissues. These are easily confused with tuberculous infiltrates and are just cause for error when remaining in the upper lung fields.

The inhalation of dusts irritating to the lung parenchyma is seen in pneumoconiosis in its varied forms. The roent-

for tuberculosis. These may be difficult to differentiate except by prolonged clinical and laboratory study.

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**Chronic Suppuration.**—The suppurative diseases, lung abscess and bronchiectasis, are usually sufficiently classical to be easily distinguished from tuberculosis. Both diseases are characterized by abundant foul-smelling sputum in their acute stage, but they may settle down into a degree of chronicity which may be distinguished from tuberculosis only by long observation and persistent study of the sputum.

Hemoptysis and hemorrhage are two very common complications of suppurative disease of the lung, often causing this condition to be diagnosed tuberculosis.

Failure to examine sputum for tubercle bacilli may lead to error in diagnosis.

E. H., a dental assistant of twenty-two years, had been perfectly well until an automobile accident. This shook her up quite badly and she believed the shock of the accident caused her to aspirate gum she had been chewing. Several days following this mishap she developed cough, fever and sputum with slight pain in the right chest, anteriorly. She did not report to a physician for a month, but loss of weight and persistence of cough, sputum and fever eventually forced her to go. Examination at that time is not recorded, but the roentgenogram showed an area of infiltration in the right mid-chest the size of a hen's egg with a 3 cm cavity presenting a fluid level. The diagnosis of lung abscess was made but no sputum was examined. The patient was examined bronchoscopically to find the gum supposedly aspirated. No gum was found, but the bronchus to the right middle lobe showed much granulation tissue. For another month the condition was treated as a lung abscess with postural drainage three times a day. At the end of that time she was seen first in our clinic. There was some spread of the process in the right lung and the sputum was loaded with tubercle bacilli.

**Boeck's sarcoid**, originally described as a disease of the skin, has in recent years become of increasing interest because of its widespread systemic expressions. Recently Pinner<sup>14</sup> has ably described its protean manifestations, and in his efforts to find an etiological factor for Boeck's sarcoid he has renamed it non-caseating tuberculosis. Other careful observers have also thought Boeck's sarcoid was due to tuberculosis but in this clinic our experience with the pathology of the disease<sup>15</sup> does not allow us to believe the evidence is yet adequate for fixing any definite etiology.

The non-caseating epithelioid tubercle, very similar to the tubercle of tuberculosis, is the basic pathology of this disease. No organ of the body seems immune from this lesion but it shows a predilection for lymphatic tissues, lung parenchyma,

genogram of this condition may resemble miliary tuberculosis or advanced fibroid disease. Granite cutting, rock drilling, electric welding, iron moulding and mining are among the dusty occupations which produce a foreign body reaction in the lung parenchyma. Those dusts containing finely divided fractions of silicon when inhaled into the lung predispose the individual to the development of pulmonary tuberculosis.

**Pulmonary Expressions of Cardiovascular Disease** — Hemoptysis and pulmonary hemorrhage, so commonly a symptom of advanced tuberculosis, are not frequent in the small and early lesion. Hemoptysis may be the first sign of a rheumatic heart with mitral stenosis that has produced no other signs of decompensation. Weiss and Parker<sup>13</sup> have discussed the pathology of this lesion. Careful physical examination should reveal the cardiovascular disease. The x-ray picture of aspirated blood, however, may closely resemble tuberculosis, though its absorption in a few days will clarify the differential problem.

Infarcts in the lung produce a confusing and varied picture. Hemoptysis may be absent in infarcts from large emboli. Pleural pain is usually exquisitely severe at some time and often entirely out of keeping with the clinical and x-ray picture. Examination of the lungs may present physical signs of pneumonia, perhaps with a friction rub, or signs may be few. The roentgenogram has no characteristic appearance, but the persistence of the x-ray shadow for weeks makes it often impossible to differentiate from shadows cast by small tuberculous lesions.

Pulmonary apoplexy with hemoptysis in older people with hypertension and advanced arteriosclerosis is not a well-recognized clinical entity. That it is a cause of pulmonary hemorrhage in the aged has appeared not infrequently in our clinic. But pathologic proof is so far lacking.

Repeated hemoptyses in the presence of a negative roentgenogram, a negative sputum and a clinical picture not consistent with tuberculosis should arouse suspicions of another etiology. Bronchial ulcerations, cancer, benign adenoma, localized bronchiectasis and cardiovascular disease should be considered as the source of bleeding. Any hemoptysis in young people not satisfactorily explained should be investigated by bronchoscopy.

discussed differential diagnostic problems having especially to do with minimal tuberculosis

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skin, eye, liver, spleen and the small bones of the hands and feet

Clinically the well being of the patient is in striking contrast to the extensive pulmonary findings by x-ray in the presence of few or no pulmonary signs. Roughly symmetrical in both lungs these lesions may have the appearance of a diffuse fibrosis or a miliary seeding with or without enlargement of the hylus glands. Roentgenograms of the fibrotic forms are indistinguishable from advanced tuberculosis or late forms of silicosis. The miliary seedings of the lung in Boeck's sarcoid cannot be differentiated from miliary tuberculosis, miliary carcinomatosis or the miliary picture of pneumoconiosis by x-ray. The clinical course is that of a benignly chronic disease with remissions and exacerbations. The tuberculin test is usually negative.

It is not certain that any patient has ever died of Boeck's sarcoid. Those cases at postmortem which show widely disseminated epithelioid tubercles may have associated tuberculosis. But in our experience with seven postmortem studies no active tuberculosis or caseation of epithelioid tubercles has been found.

A definite diagnosis of Boeck's sarcoid can only be made by biopsy of skin or lymph gland tissue. A presumptive diagnosis, however, seems justifiable in the presence of extensive x-ray findings in the lungs which are inconsistent with the good health of the patient, especially in the presence of lesions in the eye and cystic changes in the small bones of the hands and feet. An x-ray diagnosis of miliary or advanced tuberculosis which does not fit the clinical picture should lead one to suspect Boeck's sarcoid.

#### SUMMARY

We have discussed three diagnostic problems of tuberculosis. First, the diagnosis of the small or early tuberculous lesion we have shown to be dependent on a carefully elicited history, a thorough physical examination, and laboratory tests in conjunction with the roentgenogram. Secondly, the activity or inactivity of the small tuberculous lesion seen for the first time by x-ray is shown to be determined by the repeated clinical and x-ray observation of the patient. Thirdly, we have

discussed differential diagnostic problems having especially to do with minimal tuberculosis

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## CLINIC OF DR. BRONSON CROTHERS

### THE CHILDREN'S AND INFANTS' HOSPITALS

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#### HOW FAR ARE PARENTS RESPONSIBLE FOR BEHAVIOR DISORDERS IN CHILDREN?

THE creator of the term "mental hygiene" was a genius. The words suggested to distressed people that there was a scientific method for protecting people from unhappiness, inefficiency and mental breakdowns in an imperfect world. When they were further assured that childhood was the golden age for applying the method, it is no wonder that they rushed to find out about it. Neither is it any wonder that many parents have regarded child rearing with deep concern and have watched anxiously each bit of behavior as a possible threat to normal emotional development.

The last twenty-five years have been stormy ones for the enthusiasts in this field. First they had to fight against prejudice and inertia in order to get a hearing. During the first years the propagandists were not restrained very energetically by cautious advisors. They felt justified in presenting a picture in which hopes and facts were inextricably mingled. Certain slogans such as "Mental Disease is Preventable—Mental Health is Procurable" were approved. A good many people were given the impression that if anyone entered an institution for mental disease it was due to an error of medical supervision or to a mistake in education, either at home or in school. Of course no official speaker went so far as to suggest that all mental disease was preventable, but representatives of societies mentioned 50 per cent as a reasonable figure.

The response was immediate and financial support was generous. All sorts of people enlisted and various rather elaborately organized groups were set up to implement the new ideas. The leaders are now faced with the problem of distributing valid information to individuals with every kind

of background Obviously the conservative practitioner of medicine is a bit bewildered and resistant, but essentially benevolent

By now, after some twenty-five years, the results of steady campaigning have begun to appear As far as I know, there is no available statistical evidence that techniques are available to prevent mental disease on any considerable scale To that extent the aims of the campaign do not seem to have been realized On the other hand, most well-informed people are quite convinced that children whose parents are advised by individuals who are familiar with the psychological and psychiatric investigations carried on by experts, have more chance for a happy childhood and reach adult life with a better chance to achieve successful adjustment than those who have not received attention

The present situation is a difficult one A great many intelligent people accept the general theory that parents ought to be able to guarantee the mental health of their children, if they consult and obey experts This leads to a search for advisors, and obviously the family doctor is likely to be consulted about behavior which is troublesome or about general principles of child rearing Most people are correctly advised by their physicians on physical matters and their children are subjected to a series of inoculations, weighing and measuring and so on It is a considerable shock to find that the doctor deals with no such confidence and effectiveness with intellectual and emotional difficulties

It is impossible to discuss child guidance in general here without laying oneself wide open to the charge of trying one's hand at the same kind of superficial statement which is making for confusion in the newspaper articles My only hope is that certain difficulties in the field of medicine may be stated and considered

The first difficulty is that a competent study of behavior in childhood demands a shift of emphasis on the part of the physician whose interest is chiefly devoted to study of the structural body Ordinarily the physician starts with one patient He assumes that the patient, before disease attacked him, was a physical specimen practically identical with others of his age or sex, and he tends to take it for granted that the disease he is observing will run a predictable course

In trying to help parents to guide the mental life of a child, he is automatically dealing with more than one person. He has to modify his reliance on a conception of initial uniformity and he has to admit that he must expect a less predictable course.

The confusion and the resentment which frequently arise when practitioners of somatic medicine enter into discussions with some psychiatrists and psychologists is based on differences of emphasis rather than on more fundamental disagreement. Everyone who is interested must have heard exasperated psychiatrists say that doctors in general regard the human body as a test tube in which predictable reactions occur, and exasperated physicians retort that psychiatrists do not understand pathology. It seems possible that the difficulty is more superficial than it seems and that it arises around the relative values of a conception of uniformity to the internist and pediatrician on the one hand, and the psychiatrist on the other.

The internist is usually, at heart, an experimental biologist. His methods of research depend upon control experiments. In the laboratory he deals with selected strains of animals which can be depended upon to react uniformly to his experimental manipulations. He tries to control all possible variables and in general keeps out confusion. His clinical work depends upon his acquisition of a considerable number of standards to which he can refer. Out of the theoretically endless possible patterns in a microscopic slide of tissue from a given organ, he knows that only a very few occur except when disease is present. Only the most unusual disease processes alter the body enough to prevent the anatomist from using it to demonstrate normal bodily structure. Everyone who has taught medical students knows how difficult it is to arouse interest in vague problems and how easy it is to discuss clean-cut and predictable syndromes.

The medical students who find satisfaction in the experimental approach are given every opportunity for structural research and very little effort is made to enlist their interest in personality. Another group is not absorbed so completely with the closely defined problems of the laboratory and see much to interest them in the more speculative problems of behavior. To this group the idea of uniform human material reacting predictably to noxious stimuli is completely inade-

quate They conceive of the baby at birth as possessing certain innate characteristics which may be very different from those of a physically indistinguishable baby They then assume, quite obviously, that the stresses of environment will profoundly affect the development of a personality

It is no wonder that these two groups of doctors find it difficult to see problems eye to eye However, since both have received a training which has stressed respect for uniformity, they do not completely misunderstand each other The people, without medical training, who are interested in mental hygiene, may too easily accept an attitude which lays almost no stress on uniformity at all

The parent who approaches the problem of child rearing with the preconception that he or she will need expert advice at every turn is introduced at once to a conception of uniformity The weight curves, the steady supervision of a nurse, the measured quantities of food and so on, suggest that perfection depends on approximation to known standards of growth and development Later on, the nursery school and the grade schools provide standards by which the child can be judged The intellectual variations can be more or less accurately measured, but very little can be done to alter the pattern The doctor and the parent are both inclined to assume that there is some method of forcing emotional factors into a predictable pattern It is this effort, if it is made, which needs the most careful handling

It is entirely absurd to discuss the advice to be given to parents of children unless we specify the age of the child and the reasons which led up to the offering of advice The least complicated situation is that presented by the parents of a newborn infant who wish to ensure his normal development by following expert advice The citing of a case history will furnish a basis for discussion

A B was the first child of superior parents who selected their advisors with care and attempted to follow their advice The pediatrician who supervised the baby from the start held the firm opinion that parents should not show affection or tenderness to a young baby, but should preserve as unemotional an attitude as possible towards it He regarded this attitude as the best insurance against jealousy of later children The parents, being earnest and docile, curbed every impulse to make much of the child even during a prolonged period of vomiting and loss of weight The mother main-

tained breast feeding for six months and then weaned the baby according to directions. The meticulously kept record of the pediatrician shows that in every measurable way the child kept close to the prescribed standards. The family and the doctor gradually became aware of disturbing deviations from any acceptable standard in the emotional reactions of the child and they tried to force conformity by further applications of rigid routine. The doctor recognized that the birth of a sister after two years disturbed the boy and he urged the family to avoid shows of affection toward her also.

The deviations from acceptable standards continued and, at three, he was an aloof, rather cruel little boy. He would apparently crave affection and then strike out against the individual he was appealing to. This behavior, being unexpected and disturbing, was interpreted as evidence of mental abnormality and therefore a problem to be set before other experts. The child was then referred to a psychiatrist who sent him to The Children's Hospital for study. We found that he showed no important deviations from normal on physical study. His intellectual capacity was adequate, with an intelligence quotient about 120. His use of language was below, rather than above, that of his contemporaries. Our impression, gained by careful observations in the psychological laboratory, in the playroom and at meals, was that the boy was emotionally immature, intellectually superior and physically sound. It seemed obvious to a series of observers that he craved but did not know how to find security. After this study the psychiatrist, the pediatrician and the family agreed to a far more flexible routine and at the end of six months marked lessening of tension and improved behavior is evident.

This case has various points of interest. In the first place, the pediatrician was interested and intelligent. He had a routine and he had faith in his ability to enforce it. The parents accepted, literally, his advice to deal, without show of affection, with a first baby. The result was unsatisfactory and a shift of plan was made with reasonably promising chances of reaching an adequate solution.

There are several major problems for discussion. First, of course, is the question whether it is sound policy to attempt to diminish the exhibition of tenderness by a mother. The analysts, and many non-analytic psychiatrists who deal with little children, have pointed out the danger of impersonal handling of small children and there is a growing belief among pediatricians that the virtues of rigid routines have been overemphasized. Then it must be borne in mind that parents suffer if they cannot enjoy their children. It is amusing, and perhaps important to remember that grandmothers have been regarded with irritation during the period when pediatric routine was most rigid. Very probably they have saved the day for innumerable children. Certainly the acceptance of any routine



which demands curbing of such a fundamental impulse as pleasure of the parent in the child cannot be regarded lightly

If pediatricians and general practitioners are willing to take the responsibility for offering advice on all problems of child rearing, they will have to rearrange their ideas about uniformity of human material. Personally I would be dismayed if they modified these ideas too easily in regard to physical status. It seems clear that there is much to be learned about permissible variations and about growth and development, but by and large doctors ought to abandon ideas about physical standards very reluctantly.

Child management, however, involves too many people and too many variables in the child itself to make routine completely safe. Psychologists are finding standards which can be trusted so that prediction of mental performance is no longer guess work. On the whole, many patterns of behavior in adults as well as in children are known to psychiatrists.

The job which faces those of us who supervise the growth of children is to develop methods which will help parents to apply rules where they are valid, and to deal wisely with situations which cannot be reduced to rules. We are challenged to understand the trend of psychiatry, to apply principles which are within our competence and to seek advice when our special training fails us. Otherwise, we fall back too readily on the assumption that aberrant behavior is due to the fact that parents have done a poor job.

The allocation of praise and blame in this field by doctors is not too safe a matter. Even a decision as to whether the evidence justifies holding parents responsible for warping the lives of their children is a serious thing. I feel, and I am sure that many psychiatrists would agree, that pediatricians and general practitioners are inclined to carry their ideas of uniformity and predictability into areas where they are not useful. A willingness to respect variables and to admit the occasional irrelevance of the techniques of structural medicine, is necessary if the practitioner is to help parents in the emotional difficulties which inevitably arise when the individual baby begins his struggles through a confusing world.

## CLINIC OF DR. H. HOUSTON MERRITT

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### PAROXYSMAL DISORDERS OF THE CENTRAL NERVOUS SYSTEM

THE central nervous system is peculiarly susceptible to a variety of morbid conditions characterized by the paroxysmal appearance of dramatic symptoms with apparently normal function in the interim between paroxysms. Chief among such conditions are migraine, epilepsy and Menière's syndrome. These conditions are not disease entities but clinical syndromes. Structural abnormalities of the nervous system may or may not be present, but such abnormalities, when present, do not explain the attacks, because they may be and often are present without the occurrence of the typical paroxysms.

The cause of the attacks must be sought in pathologic physiology rather than in histologic pathology. Advances in the understanding of the pathologic physiology underlying these conditions have been very slow, and it cannot be said that we have as yet the answer to any one of the three. It is the purpose of this article to discuss briefly some of the advances that have been made and the application of the results to the treatment of these conditions.

#### MIGRAINE

Migraine is a symptom complex characterized by recurrent attacks of headache, often hemicranial in type, associated with visual and gastro-intestinal symptoms and with a tendency to a familial occurrence. Rarely, the headache may occur without the visual or gastro-intestinal symptoms, but the diagnosis is insecure unless there is a history of typical migraine attacks in other members of the family. The headaches may be generalized or localized to one portion of the head, they increase

in intensity and usually incapacitate the patient. Nausea and vomiting are almost constantly present, the visual symptoms, scintillating scotomas with or without hemianopia, are less frequent. The duration of an attack varies from a few hours to a day or more, and the frequency from once a day to several times a year. Women are more often affected than men and attacks are often associated with the menses. Rarely, the symptoms may be recurrent bouts of nausea and vomiting without headache (abdominal migraine).

The list of conditions<sup>1</sup> which are said to be the cause of migraine is long, but no one cause satisfactorily explains the symptoms except in a small selected group of cases. Possibly there is a common underlying pathologic physiology in all patients with migraine headaches regardless of the cause. It has been suggested by Graham and Wolff<sup>2</sup> that the headaches are produced by a stimulation of the cerebral periarterial nerves by pulsations in abnormally dilated vessels. On the basis of this hypothesis the therapeutic effect of ergotamine tartrate,<sup>3</sup> which had been empirically used for several years for the relief of an attack, is due to a constriction of these dilated vessels. If it can be proven that this is the correct explanation of the mechanism of the migraine headache, it may be possible to produce permanent freedom from attacks by operative interruption of the impulses arising from the abnormally stimulated periarterial nerves by ligation of the middle meningeal or other branches of the external carotid artery. Such operations<sup>4, 5</sup> have been tried in a few cases, and while the reported results have been promising, they have been too few to draw any definite conclusions. It must also be emphasized that this hypothesis as to the cause of the migraine headache does not get to the ultimate basis, since it does not explain why the arteries are dilated and allow the periarterial nerves to be abnormally stimulated. Perhaps the answer lies in some altered disturbance of the chemical control of these vessels.

### EPILEPSY

As stated before, epilepsy is not a disease entity but a symptom complex characterized by the periodic occurrence of transient disturbances of consciousness, with or without convulsive movements. Such a definition is inadequate, since the disturbance of consciousness may be so slight that it cannot

be detected by superficial observation even though convulsive phenomena may be present. Recurrent attacks of loss of consciousness may occur in conditions not included in the category of epilepsy.

Epileptic attacks may be divided roughly into three groups: petit mal, grand mal (including jacksonian), and psychic equivalent or psychomotor attacks. In *petit mal* attacks there is a transient clouding or loss of consciousness lasting for only a few seconds, with or without minor movement of the head, eyes and extremities, and loss of muscular tone. *Grand mal* attacks may be ushered in by a warning (aura) and are characterized by a sudden loss of consciousness followed by tonic and clonic spasms of the musculature, with or without urinary or fecal incontinence. The force and distribution of the tonic and clonic contractures are subject to a great deal of variation, and the duration of an attack may vary from less than a minute to many minutes. The attack may be followed by a post-convulsive stupor or mental cloudiness, headaches or transient paralysis.

*Psychomotor attacks* or *psychic equivalents* are terms used to describe a heterogeneous group of epileptiform disturbances which do not conform to the classical grand or petit mal types. Psychomotor attacks are much more common than is realized. Unless the attacks are witnessed or a complete description of them is obtained, they are usually labeled as petit mal attacks. They differ from petit mal attacks in two main respects. First, their duration is usually very much longer. Loss of consciousness in petit mal is usually only for a second or more while, in psychomotor attacks, consciousness is often disturbed for from one-half to two minutes, and occasionally for as long as an hour or more. Secondly, muscular movements in petit mal are clonic, usually involving only eye or facial muscles. Psychomotor attacks are usually accompanied by tonic or coordinated, more or less purposeful movements such as picking at clothes, taking off shoes, shuffling feet and the like, and occasionally complicated, apparently purposeful acts are performed without the patient having any knowledge of performing them or any recollection of the act after consciousness returns. The patient may talk during the attack, but a connected conversation is not possible. The patient does not understand what is said to him or respond intelligently.

The stated causes of convulsive seizures are myriad<sup>6</sup> and they vary from fixed cerebral lesions to disturbances in body chemistry. Some understanding of the mechanism of the action of these varied causes of convulsive seizures has been offered by an analysis of the electrical potentials of the cerebral cortex by the electro-encephalograph. It has been shown by Gibbs and Lennox<sup>7 8 9</sup> that with the seizure there are disturbances in the electrical activity of the brain characteristic for each of the three typical forms of convulsive seizures, regardless of whether the seizure is presumably caused by a

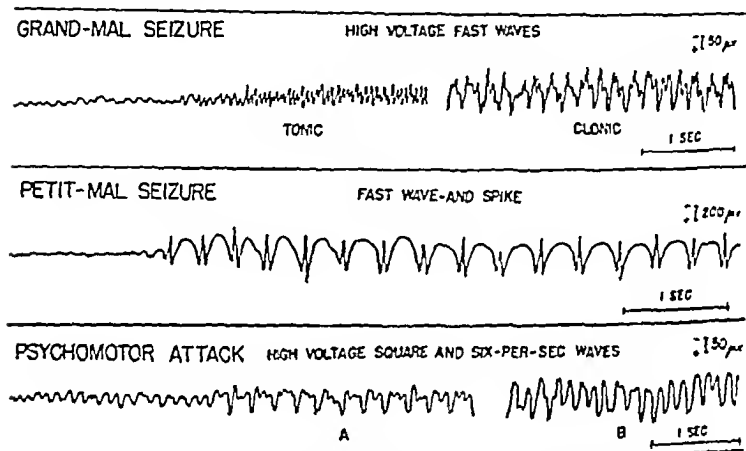


Fig 79—Example of electro-encephalographic records of patients before and during epileptic seizures. The first portion of each record shows the normal cortical activity for each patient and is followed by abnormality characteristic for the type of attack as labeled. (Courtesy of Dr F A Gibbs)

brain tumor, cortical birth injury, or a disturbance of the blood sugar or calcium level. The electro-encephalograph is not only of value in recording the changes that occur coincident with attacks, but also in registering characteristic short bursts of abnormal activity in the interval between attacks. Examples of the abnormal cortical activity in the various types of convulsive seizures are given in Fig 79, which was furnished by Dr F A Gibbs.

In petit mal attacks the cortical potential becomes slower and of much greater voltage, with the formation of large slow waves and an interposed spike, at the rate of about 3 per

second. These abnormal 3 per second waves and the typical petit mal attack are peculiarly susceptible to changes in the carbon dioxide content of the blood. Hyperventilation, with the blowing off of carbon dioxide, will precipitate the abnormal wave activity and cause an attack.

At the onset of a grand mal attack there is a great increase in the electrical activity of the cerebral cortex, with fast high-voltage waves at the rate of 15 to 30 per second. In the tonic and clonic phase of the attack these waves become much slowed, to about 6 per second, and of even higher voltage. These waves decrease in intensity and there is an almost complete cessation of cortical potentials in the post-convulsive stupor with a gradual return to normal with recovery. Grand

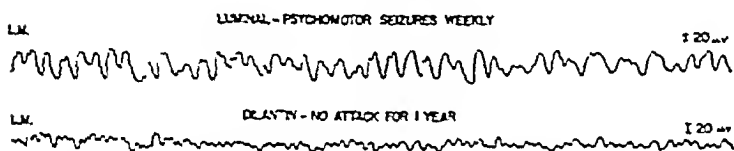


Fig 80—Electro-encephalographic record of the activity of the left motor cortex of a patient with frequent psychomotor attacks is shown in upper line. The record in the second line is from the same patient one year later. In the interval between the two records the patient had been entirely free of attacks while under treatment with dilantin—sodium diphenyl hydantoinate. (Courtesy of Dr W G Lennox)

mal attacks and the typical electro-encephalographic changes can seldom if ever be precipitated by hyperventilation.

In psychomotor attacks there is an increase in the electrical activity of the cortex, with the formation of large square-topped waves at the rate of 4 to 6 per second without the interposed spike as seen in petit mal attacks.

The information obtained by the study of the electrical potential of the cortex is a great step forward in the understanding of the pathologic physiology of "epilepsy." Studies of the factors producing changes in these potentials will possibly lead us closer to the actual solution of the cause of the seizure. Of more practical importance at present is the application of this technic to the diagnosis and subclassification of the types of epilepsy and as a guide to the therapy. An illustration of the changes in the brain waves coincident with improvement under therapy is shown in Fig 80.

## MÉNIÈRE'S SYNDROME

Ménière's syndrome is a syndrome characterized by recurrent attacks of severe vertigo, with nausea and vomiting. The onset of attacks is usually acute, and sometimes occurs with such violence that the patient is plunged headlong to the ground. The duration of individual attacks varies from a few minutes to a day or more and the frequency of the attacks from several a week to once in a year or two. Tinnitus is usually present during the attack and may be present in the interim between attacks. Impairment of hearing of the nerve type is usually present.

Examination of the patient during an attack or in the free interval usually reveals no significant abnormalities except those resulting from a disturbance of the auditory and vestibular portions of the eighth nerve. Usually, only one of the eighth nerves is involved, but occasionally the disturbance is bilateral. The diagnosis of the condition is not difficult, since the typical clinical picture is rarely simulated by any other condition. There is no known adequate pathology since histologic studies of these cases are rare and nothing of significance has been reported.

The first advance in the understanding of the pathogenesis of the attacks in Ménière's syndrome was the suggestion that it was the result of a disturbance of the water and salt equilibria.<sup>10</sup> On this basis a dehydrating and acid-forming diet (low salt intake with ammonium chloride by mouth) was introduced as a therapeutic measure,<sup>11 12 13</sup> which resulted in a relief of the symptoms in a fairly large percentage of the cases. More recently it has been shown that there is a relatively high potassium content in the serum of these patients.<sup>14</sup> It was reasoned that the high level of potassium in the serum was an indication of a depletion of this element in the tissue cells (similar to the high level of serum calcium in regard to its storage in the bones). This led to the giving of a normal diet with large doses of potassium<sup>15</sup> by mouth, with results that are fully as good and perhaps better than those obtained with the low sodium diet and ammonium chloride.

## DISCUSSION

There may be a great deal of disagreement as to the propriety of grouping three such syndromes as migraine, epilepsy,

and Ménière's together. Their chief feature in common is the paroxysmal nature of the attacks with little or no symptoms in the interim between attacks. The presence of a pathologic lesion in epilepsy and in endocrine or other disturbances in migraine, and disease of the eighth nerve in Meniere's syndrome, does not explain why the attacks occur at one time and are not constantly present. It is possible that the mechanism of the precipitation of the attack is similar in all three instances and that the focal point of the disturbance and the resulting symptom complex or seizures are conditioned by the underlying pathologic disturbance.

It cannot be said that we have as yet determined the mechanism of the precipitation of the attack in any one of these three conditions, but rapid advances have been made in the last decade which give us great help in the medical therapy and hold promise for the ultimate solution of the problem.

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## CLINIC OF DR JOHN P MONKS

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#### HUMAN AND SOCIAL FACTORS IN CARING FOR PATIENTS

It has become increasingly apparent to physicians in this country, especially during the last decade, that many factors occur in the care of patients which seem to fall outside the realm of the formal science of medicine as it was taught them in medical school. These might be called the "human" and "social" factors in medicine.

In an age that is now past in the cities, and which is already radically changed in the country, the practicing physician saw his patient in his normal and usual environment. After a few years' practice he knew intimately, not by formal study but by the closest physical contact, his patient's ancestry with its predilections for or freedom from certain diseases or traits of character, he knew about his upbringing and schooling, good, bad, or indifferent, he knew the members of the family, both those living at home and those elsewhere, and he knew much about those who had died. He knew all about the details of his patient's occupation, whether that particular work was what the patient really wanted to be doing or whether he had been forced to do it by his family or by circumstances. He also knew of the existence of any potential occupational hazards, either physical or mental, and all about his patient's financial situation, and his mental and physical habits. In short, he knew very accurately and in great detail what sort of a person the patient was and in what sort of an environment he lived. His knowledge of all these factors usually far surpassed his knowledge of so-called "scientific" medicine.

At this point it may well be asked, "Well, what if he did know about all these things. With our scientific knowledge

can we not do much more for the patient than he did?" Such a question is entirely appropriate and timely, and this paper is an attempt to give an answer to that question.

I believe the answer to be as follows. We, as physicians, are in a position today, owing to the increase in scientific knowledge, to do far more for our patients than were the practitioners of the past age. We are, however, not utilizing a considerable part of the knowledge that already exists in the ill-defined human and social field of Medicine, whether it be in history taking, diagnosis, treatment, or prognosis.<sup>1</sup> This knowledge to a great degree has been neglected by present-day physicians, and it has even been somewhat looked down upon by a few, as it is of a nature exceedingly difficult to subject to scientific experiment and proof.

The reason that the medical profession once possessed some of this knowledge and then lost it, only now to be in the process of slowly and painfully reacquiring it, is I believe due to the following reason. The majority of current teaching in medical schools is carried on within the four walls of a medical school or hospital. Every patient appears projected against what is, for him, a distinctly abnormal background. It should not be forgotten that the average patient's familiarity with disease and hospitals is somewhat equivalent to the average physician's familiarity with legal difficulties and law courts, or labor disputes and industrial plants. In other words, the knowledge is usually only slight and sporadic.

It is, therefore, very difficult for medical students to acquire a true picture of what sort of a person a patient truly is when seen against an abnormal background. Such students have not seen, for example, the young executive in a highly responsible position gobble his breakfast, take no time to go to the toilet, rush to his office, and spend the day in a clamor of telephone calls, dictation, interviews, and meetings, only to return home just in time to dress for dinner and spend a late evening in a hectic social whirl. An electrocardiogram, a teleroentgenogram of the heart, and consultation with a cardiologist would not be needed in the investigation of the sub-sternal pressure of which this patient complains if they only had the picture of the patient's daily life before them. This patient's heart proves to be entirely normal, as does the rest of the physical examination.

Nor have they seen the large old house, for example, the home of a boy of eighteen, which is so shabbily kept that he is ashamed to entertain his friends there. He, not liking to accept hospitality without reciprocating, retires within himself and develops symptoms of loss of appetite and weight, listlessness, and easy fatiguability. His physical examination likewise shows nothing abnormal.

As a result of specialization in medicine in many of the hospitals in which physicians are trained, the investigating and dealing with such comparatively simple medical problems as the above are left to the psychiatrist or the hospital social service worker. They are both trained in these matters, though from somewhat different points of view. When, however, a physician has finished his internship or residency, he finds himself without the aid of a social worker in his practice in the community. He is then faced with the realization that part of his education has been so neglected that he cannot, for example, discover that the reason why his patient, a young college student, has headaches and is in danger of being expelled from college is that he and his girl are quarreling over some trivial matter. He has to refer such a case to a highly trained and highly paid psychiatrist, who may be far less well equipped to cope with all the factors involved than the physician himself. He may then commit the mistake once made by an ophthalmologist, an orthopedic surgeon and one or two other specialists, whom a young wife consulted on her own initiative without reference from her own physician for symptoms of fatiguability in one or the other systems of the body. Each one of these prominent specialists, viewing the problem only from the point of view of his own particular specialty, prescribed rest as the keystone of their therapy. Following such advice this patient steadily became worse, and it was not until she came into the hands of a physician who had the vision to regard her as a whole human being and not as a loose collection of ophthalmologic, neuromuscular, and other symptoms, that the truth of the matter appeared without any great difficulty. Resting was what the neurasthenic young wife had been doing in far too great a degree all of her life, and what she really needed was insight into her various problems, from which she had retreated subconsciously, assuming the mask of fatigue to escape having to cope with them.

Unless the physician recognizes that all the factors of a patient's illness, personal characteristics and environment may have to be taken into consideration, he commits the error, all too frequent in hospital practice, of transferring a patient with heart disease and under digitalis therapy, for example, to the surgical ward for some minor operation, and on the latter's discharge from the hospital the fact that he has heart disease has been forgotten. Later, the patient's heart becomes decompensated, as he had not been given a prescription and directions for taking digitalis on his dismissal from the surgical service and as he had never received instructions regarding restriction of activity and regulation of his habits of life.

In the case of the woman worn down by a long siege of illness, the physician grasps at the opportunity suggested of having her rest for several months on a nice quiet farm in the country. But if he has not investigated, he does not realize that a rest of several months on this "nice quiet farm in the country" involves at least two months of really cold weather, and that the farmhouse in question has only two of its rooms heated by oil stoves, and that the room which the patient will occupy is not one of these but is in an unheated wing of the house. Also, washing and toilet facilities are most primitive, and the kind owner of the farm has her hands full with a family of noisy children, and the food supply from the neighboring town is not infrequently interrupted because of snow drifts.

Furthermore he tells patients to "take it easy for a while" after a debilitating illness, and their interpretation of this direction is to do nothing for a week, or for a day or two of normal temperature, and then immediately to resume full activity with the all too frequent relapse resulting. He tells a young man as he treats his peptic ulcer that he must not worry, little realizing that the mortgage on the latter's house is about to be foreclosed.

Obviously in each patient's life there may be many undesirable factors which cannot be eliminated and which have to be tolerated. The physician must not, however, consider his task well done until he is certain that he is in possession of all the pertinent facts, and that everything possible has been done.<sup>2</sup> Otherwise, his advice is liable to be unsound, or the patient cannot or will not follow it.

At this point imagine the physician at his office desk when a patient appears. The reason why this particular patient appears at his door and not at some other doctor's may be any one of many different ones, some important, some not.<sup>3</sup> Unfortunately we have not the time to go into them here. Suffice it for the moment to say that the patient is at the door and that he is there because he is suffering from some symptom or from some group of symptoms (I have deliberately avoided saying that he was suffering from some disease). He is there because something troubles him and he can't set it right, and he therefore comes to the physician to do it for him.

From the patient's point of view he is suffering from such symptoms as loss of weight and appetite. From the physician's point of view he is suffering from a disease which may prove to be carcinoma of the stomach or an anxiety neurosis, either of which may be the cause of the symptoms. The two of them are therefore approaching the problem from different points of view. An appreciation of this fact is important. Part of the physician's job is therefore to explain in a way comprehensible to the patient, or to ascertain that he already understands, why it is necessary to do this, that and the other thing—in other words to make a diagnosis before doing what he came for, namely relieving a symptom. Now the "this, that and the other thing" usually occurs in obtaining the history or in employing diagnostic or therapeutic procedures. Seldom does it seem to fall in the realm of the physical examination. Few patients have to be shown the necessity for even a most painstaking physical examination. This is taken for granted, in fact, lack of thoroughness in the physical examination can call down far more criticism on a doctor's head than lack of a careful history.

It is in this latter field, that of history taking, that present-day physicians often err badly, as they do not know, as did the old-time physician with a geographically concentrated practice, the family, marital, medical, occupational and social histories and habits of the majority of their patients. Today, these facts have to be found out, usually by asking questions, and these questions are frequently never asked. The opportunity for personal observation is limited by the modern custom of seeing patients far more often in the office and hospital than in the home.

For instance, take the case of the secretary of an extremely busy, financially and medically successful doctor who had always worked at a high pitch of activity which he subconsciously imposed on all around him. This secretary had for years been doing the work of two or three trained persons. She had worked long hours and was suffering from increasing and serious symptoms of exhaustion. The presenting symptom was headache, so x rays of the skull were taken and a lumbar puncture was done at the instigation of her employer when her headaches came to his notice. The secretary's personal physician, who knew the true history of her occupational stress and strain as well as her various financial and family difficulties, only with the greatest difficulty persuaded her employer that the real cause of her trouble lay in these fields. Treatment of the underlying cause, overwork, by a prolonged vacation eventually restored her to her normal good health and safeguards were provided for the future.

Here we see the difference between the value of the opinion of the doctor who was himself so involved in the patient's illness that he was unable to evaluate the various factors present, and that of the doctor who took care to inquire carefully into details of the patient's life and could view the situation impersonally.

#### COMMON SOCIAL FACTORS ENCOUNTERED IN PRACTICE

Let us now consider some of the more commonly encountered social or human factors which play a part in the problems of the patients one meets.<sup>4</sup> Inasmuch as clinical problems are all dealt with according to the familiar sequence of chief complaint, present illness, family history, marital history, past history, occupational history, social history, habits and personal characteristics, physical examination, laboratory examination, diagnosis, treatment, and prognosis, though the exact order may differ somewhat, I shall give examples of cases in which the points I wish to emphasize fall roughly under one or more of these headings.

A student in the senior class entered a college health department and requested a physical examination to be sure that he was in "good shape" on leaving college. This college required a compulsory physical examination on entering in the freshman year and students were encouraged to be re-examined yearly. Many students took advantage of this opportunity. A complete examination of this particular student showed no significant abnormalities, but the examiner pressed the student for the real reason for his having requested the examination. A slight hesitancy in the student's answers then led to further questioning. He did not give a satisfactory answer, he admitted he was

trouble involved but as to what the cause of this was he did not wish to say. He was persuaded to talk it over with a psychiatrist, who later reported the boy to have been on the verge of a complete "nervous collapse" due to a severe sexual excess of several years standing.

This case illustrates how easily a serious mental difficulty might have persisted had not the student's reason for requesting the examination been questioned. The chief complaint as given by the patient often is quite different from that which actually bothers him most.

A twenty-seven-year-old American housewife entered the wards of the Massachusetts General Hospital with the complaint of having had diarrhea for three weeks and more recently of having vomited. It appeared after careful questioning that for several years she had done arduous mill work for six and a half hours daily. On returning home at night, she had then done all the housework, which included all the cooking, housecleaning, washing and ironing, entirely unaided, for seven other members of her family, who lived with her. Only one of these seven was a child of hers. One of these seven was a twelve-month-old child of twenty-six, another was the coughing and complaining father-in-law who has a chronically ulcerated ear. All eight lived on \$12.00 a week, half of which the patient earned herself. Much of her childhood had been spent with six brothers and sisters and her mother in traveling from town to town attempting to follow a father who had regularly deserted his family. Tuberculosis had always existed. X-Rays showed advanced bilateral pulmonary tuberculosis and enteritis, probably tuberculous. The prognosis in this case was poor. Had this unfortunate family situation been discovered earlier, adequate protection from the father-in-law, the probable source of her infection with his subsequently proved tuberculous sputum, and have been provided as her infection seemed of comparatively recent origin. Also help in her work by available public or private social agencies would have eased some of the crushing burden from her.

This case demonstrates quite clearly that though the anatomic diagnosis was tuberculosis the actual underlying and basic cause of the patient's difficulties was the familial and financial situation rather than the tubercle bacillus. Help for this patient probably came too late but it is quite clear what should have been the proper treatment had the patient been seen before she had developed advanced tuberculosis.

A middle-aged housewife entered the wards of the Massachusetts General Hospital with an easily recognizable myxedema. A keen medical student diagnosed, however, that her irritability and nervousness for the preceding two years, a symptom typical of the disease, had caused her family to fear that she was losing her mind. Her husband had begun drinking heavily in



exasperation at his wife's changed temperament, and friction had developed in the family—all directly traceable to the patient's symptoms. The husband had not visited his wife in the hospital until asked to do so at the student's suggestion, and then it was explained to him that all the patient's nervous difficulties had been due to her disease and to no other cause, and that they would vanish completely in a short time. Realizing the truth for the first time and seeing the great change that had already taken place in his wife's condition, he immediately stopped drinking and the family relationships once again became harmonious.

Here is shown quite clearly that there was more to the successful treatment of this patient than the daily dose of thyroid, and that it was accomplished by obtaining a complete and detailed "family history," and acting on the information obtained.

A not unusual problem presented itself in regard to the occupation of a man in his fifties who had had attacks of angina pectoris. He was a locomotive engineer, and it was felt after considerable discussion that the responsibility of the hospital to which he had been admitted was not limited only to the appropriate treatment of his cardiac condition. With the patient's consent, the whole matter was therefore taken up with his employers, the railroad, who agreed that the danger of his possible sudden death made it advisable to shift him to another job more sedentary in nature and where, if he collapsed, others' safety would not be endangered. This was done and the patient continued to earn his livelihood and did not lose his eligibility for a future pension.

A young business man of twenty-five entered a doctor's office complaining of pain in his abdomen of such a character that a peptic ulcer was suspected. The x-ray showed the presence of a duodenal ulcer. Treatment of this condition by diet, powders and general advice was only partially satisfactory. The doctor next heard of his patient when a urologic colleague informed him that the patient had come to him complaining of sexual impotence. Treatment by bromides and a polyglandular preparation was instituted by the urologist, but without any success. Finally, as the patient became worse, he consented to tell what he had been ashamed to formerly, due to a false sense of pride, and the following story was pieced together by the physician. This patient had been brought up in the most luxurious surroundings, having been given everything he desired without a question as to the cost. His wife, whom he had married when they were both quite young, had been brought up to practice fairly strict economy. Neither of them had perceived the necessity for adjusting their points of view after marriage. He had been working in a family business, and though possessed of real ability in certain directions, had been conscious of "riding on his family." Both husband and wife had been brought up in complete ignorance of the sexual relationship and intercourse had eventually become impossible due to her increasing frigidity and his developing impotence. Their three

children had been brought up in an atmosphere of constant friction and wrangling, and they reflected it in their behavior. The patient's mother constantly interfered in her daughter-in-law's life. When the patient had entertained thoughts of suicide and was psychologically "flat on his back," it was finally possible to persuade him to go to a psychiatrist. This was done since the physician, though he knew all the facts, felt successful therapy was beyond his own abilities. After a year or more of regular interviews with the psychiatrist the whole picture changed in most of its aspects. There was far more happiness, harmony, and understanding between husband and wife, sexual intercourse became satisfactory to both, the children's behavior improved, and he gave up his job and entered another business, in a much lower capacity than formerly but where he was doing what he did happily and entirely through his own efforts. Also, the symptoms caused by his peptic ulcer showed steady improvement.

The implications in this case are quite obvious, namely, that the treatment of either the ulcer or the sexual impotence was completely without result so long as the psychologic factors caused by the patient's background and family life were not taken into consideration.

#### MANAGEMENT

In these case histories I have given are samples of the factors which arise in everyday problems encountered by all doctors in their clinic or private practice. The conscientious doctors discover them, other never know they exist. Hence it behooves us to become more intimately acquainted with this general field.

The sources of sound information in this field are few and far between. A few medical schools have recognized their responsibility, and lectures and courses have been scattered at various points throughout their curricula.<sup>5 6 7</sup> At present, the best opportunities to acquire information are in observing physicians who are interested in this field handle patients in a hospital. Personal experience, as in all else in life, is invaluable. The "literature" on the subject can hardly be said to exist. Most characteristic of it is the fact that articles appear widely scattered through the literature of general medicine, preventive medicine, psychiatry, medical education, sociology, and especially that of the hospital social worker and the recently created industrial sociologist.

**Interviewing the Patient**—For the physician already practicing, the acquisition of a particular point of view, if he

does not already possess it, is often most difficult. This point of view consists essentially in regarding the patient as a normal person temporarily or permanently out of keeping with his accustomed background and not solely as an isolated case of some pathological entity. Next comes a search for facts. The familiar routine system history (head, eyes, ears, nose, throat, etc.) follows. At some appropriate point in the history (which may differ in each case, whether after the present illness or at the very end of the past history), a technic different from the usual history taking should be employed. This for want of a better name can be called "interviewing." During the usual physical history taking, one has proceeded very much on a basis of questions such as "Where was the pain located and what was it like? How often did it come and how long did it last?" And so on. In other words, the patient has been led on from one question to another.

In the interview, which usually deals with the fields of family, marital, social and occupational relationships and matters of upbringing, education, personal characteristics and habits of thought, the technic is totally different. First of all the physician must either seek elaboration of some item in the physical history which naturally leads into these fields, or he must give a convincing reason to the patient that discussion of these topics is desirable.

There are many ways of showing this desirability, and these differ in each individual situation. One method is for the physician to express the following idea in his own language: "You have told me all about the symptoms which trouble you and you have answered my questions about various parts of the body. Now, inasmuch as physicians know by experience that what goes on at home, at work, or elsewhere, and what characteristics people possess, frequently has an important bearing on producing such a picture as you present, I should like to discuss some of these matters with you." The physician should then endeavor to discover the presence of any factors of potential or actual importance in the various fields with which the interview is concerned, or should satisfy himself that there is nothing in these fields that needs further consideration. Potential factors of importance are many.

There is no one best way of exploring the various fields but one should follow whatever appears to be a logical progres-

sion in each case. Once started, the physician should not lead the patient by direct questioning, but should allow him to talk about what he wishes without interruption until the patient encounters a seeming stone wall or the content of a field appears to be sterile. Obviously this may prove to be difficult with a garrulous patient. However, the mere fact of garrulousness may be important.

This method of interviewing, which in many cases is most helpful, has not generally been utilized by physicians except psychiatrists. It is part of the education of hospital social workers, and recently it has been developed in the Harvard Business School for the purpose of industrial interviewing.<sup>8</sup> Five simple rules for interviewing are given

- "1 Give your full attention to the person interviewed, and make it evident that you are doing so
- 2 Listen—don't talk.
- 3 Never argue—never give advice (This, quite obviously, if translated into rules for the physician, would be, "Withhold your advice until all interviewing is finished.")
- 4 Listen to
  - a What he wants to say
  - b What he does not want to say
  - c. What he cannot say without help
- 5 As you listen, plot out tentatively and for subsequent correction the pattern that is being set for you. To test, summarize what has been said and present for comment. Always do this with caution—that is, clarify but don't add or twist."

Further, everything the patient says should be taken as a symptom. The rightness or wrongness of the patient's judgments or the content of his beliefs is unimportant for the physician except as it relates to the patient's history and his present situation. This relationship is what matters.

Haste on the physician's part is absolutely incompatible with good interviewing, and such interruptions as by the telephone should be reduced to an absolute minimum. An atmosphere of quiet and continuity is a great aid to good work. Physicians may differ in their ability to work under stress and with interruptions, but there are few patients who are not affected unfavorably by such an atmosphere as this.

Unfortunately, many lay persons and even physicians believe that a few questions, a physical examination, and a

written prescription with a few directions is adequate. It is not and never will be, unless the physician already knows all about his patient from past visits. Probably not more than an hour, or possibly an hour and a half, should be devoted to a patient except under unusual circumstances. This limit should be set, since both the physician and patient tend to tire about this time and the efficiency of one or the other becomes impaired. This is an individual matter, however, but the fact that psychiatrists seldom see patients routinely for more than an hour at a time is evidence in favor of this limitation.

The interview is therefore an essential part of every well-handled case. It may take a few minutes, or many hours. It may yield no important information, or it may be the most important contact with the patient. It often cannot be included with the history and the physical examination in the same visit. Multiple visits may be necessary to obtain a good interview.

**The Social Relationship of Patient and Physician.**—A fact seldom realized by physicians themselves is that, just as any contact between two persons in life is a social relationship and the individual characteristics of the participants reflect themselves on that relationship, exactly so is a patient's visit to a physician a social relationship, although of a particular kind and with the two participants playing very different roles.<sup>9</sup> The physician's own characteristics and habits reflect themselves on that relationship either favorably or unfavorably just as much as do the patient's. A good "bed-side manner" is solely an example of a favorable relationship. It has gained a bad name because it has been used in certain instances to hide a lack of professional competence. Certain physicians who are professionally competent are unable to "hold" patients who come to them because of some personal characteristic or habit unfavorable to the social relationship. In rare instances it will be found that a physician and a patient, due to clashing personal characteristics, had far better part company. Usually the patient attends to this, but the physician should do so on occasions if he has the best interests of his patient at heart. Often what happens is that there may be a certain clashing of personalities at the onset, but that with time this completely disappears. The commonest example of this is in the case of the young physician who takes care of the

patients of an older physician, either in the latter's absence or in the event of his death. Patients naturally find the younger man's methods somewhat different because of his youth and the different type of training each had undergone. At first patients might resent this change in method, and not realize that the younger man did not know them and their backgrounds as well as did their old physician. With tact and care, however, the younger man can usually soon establish a satisfactory relationship.

**The Physical Examination**—After the history and a picture of the background are obtained, the physical examination follows. Physicians often subconsciously create an unfavorable relationship with the patient during the physical examination. Some of the commonest causes of this are too abrupt a depression of the tongue with a depressor during examination of the throat, causing unnecessary gagging, unnecessary exposure of the patient in a cold room, and the application of cold hands or a cold stethoscope to the skin, requesting such rapid and deep respirations during examination of the lungs that dizziness results, pumping up the cuff of a sphygmomanometer or the insertion of the examining finger in the rectum or vagina without giving the patient warning that some pain will result, leaving female breasts and genitals exposed longer than is needed for adequate examination without realizing that such a factor as genuine feminine modesty still exists, unnecessary or abrupt pressure applied to the abdomen in attempting to palpate liver, spleen and kidneys. A habit of consideration for the patient's feelings in the physical examination can be cultivated, and more information can frequently be obtained from the examination under these circumstances. Laboratory examinations are entirely impersonal, but the procedures of venipuncture, lumbar puncture and certain x-ray examination can be intensely personal, as the possibility of pain is involved.

**Making the Diagnosis**—I shall next consider what to many physicians is the crowning glory of medicine—diagnosis. Unfortunately, most medical education has attached to diagnosis an importance of a degree it refuses to accord to other intellectual medical processes, such as treatment and prognosis. Medical education does not actively attempt to belittle treatment and prognosis, but so much emphasis is placed on diag-

nosis that most young physicians consciously or subconsciously regard treatment and prognosis as anti-climaxes to diagnosis. The reason for this attitude is easy to perceive. It is the same reason as I have mentioned previously as causing a knowledge of the physical factors of illness to be raised to a point of undue importance above psychological and social factors, namely, that the physical factors can be more easily analyzed by available scientific criteria. Just so can diagnosis be subjected to scientific test and proof more easily than treatment, and far more easily than prognosis. But do not think for an instant that I am minimizing the importance of diagnosis, for it is one of the corner-stones of medicine. There are, however, other corner-stones of equal importance. I mention this here because, to the patient, certainly the diagnosis means far less than the treatment and the prognosis, and it is well to remember that one's usefulness in practice to his patients is what is accomplished either by treatment or advice, even if the diagnosis is not at all clearly pigeonholed in one's mind. With many patients one may never make an accurate diagnosis, no matter how much one tries, but nevertheless one will be able to alleviate much suffering through treatment and advice.

**The Prognosis** —We will assume, however, that an intellectually acceptable diagnosis has been made and that one is then confronted with prognosis. Handling this corner-stone of medicine with skill has been called the highest intellectual achievement in medicine. Whatever it is, it is one of the hardest learned of medicine's secrets, for by its very nature it calls for much experience and knowledge of the ways of man and his illnesses, it can only be learned by careful personal observation, and rarely from books. It often depends on such intangibles or minute details or individual characteristics that it takes the keenest of minds to grasp them and translate them into terms understandable to the patient.

I well remember a hulking Irishman in the wards of the Massachusetts General Hospital. He had what was thought to be a very severe case of chronic nephritis, with edematous ankles and face and urine specimens loaded with albumin, pus blood and casts, and a moderately high nonprotein nitrogen level in his blood. Treatment was unavailing and he was sent home to a sedentary existence and, in the minds of the staff, to certain death within a short time. Five years later I re-

member making the following note on this man's out-patient record, "This man today is the picture of health, without a complaint of any sort, his urine is entirely negative, his work consists of pushing around 200 pound slabs of beef all day, and he says he never felt better in his life." Later, the recurrence of some of his symptoms and the reappearance of abnormal findings in his urine did not alter the fact that we had originally made an extraordinarily inaccurate prognosis as to the outcome of what had proved to be a severe episode of acute nephritis.

Inaccurate prognoses are fairly common, unfortunately, as the often-heard tale in lay circles "the doctors had given him up, but he fooled them all" would show. "Guarded prognosis" is a term used with much justification, for we are far from knowing with any degree of accuracy the outcome in many cases. We rely on statistics, on "hunches," but usually we give a prognosis with a mental reservation. Unfortunately, even when we have no mental reservation, unforeseen tragedy sometimes occurs, as in the case of the elderly man who had had his obstructing prostate gland removed without complications and comparatively little discomfort and who was sitting in a chair dressed, waiting to be taken home from the hospital. On rising from the chair he pitched forward onto the bed, dead from a coronary thrombosis, later proved at autopsy. No one had suspected up till then that there was anything amiss with his cardiovascular system. We are human and we all make mistakes, but we should seek to learn by each one we make.

In the freshman class at Harvard College hardly a year goes by without the examining physicians encountering half a dozen men with entirely normal hearts who have been previously told that they must be careful in the physical exercise they engage in because of cardiac damage in the past or the possibility of it in the future. In the cases of some of them it is a question whether they ever had any trouble whatsoever in the past, and in the cases of all of them their susceptibility to future cardiac damage is no greater than with all the rest of the students. A prognosis of the sort originally given these students may be far worse than an unduly optimistic one, as the conditioned thinking created in a young man who believes he must be careful of his heart has often had severe repercussions in his social relationships with the world. It is some-



times only after much effort that confidence is restored in these cases and these men are able to participate in athletics and lead normal lives

**Problems in Treatment**—Next we are confronted with another corner-stone, full of social implications—treatment. Before we consider this it is well to remember the Aesculapian motto "We bandage the wound, God heals it" Try and enumerate the specific cures we know in medicine. They are very few. Happily, the number of these is growing. Specifics are the mile-stones of medical progress. The existence of only a few specifics of necessity makes the majority of treatment symptomatic. One should not scorn an ability to administer symptomatic treatment successfully, for the function of the physician is a double one, to cure and relieve suffering. The latter function should not be neglected because we may be impatient at the slowness of discovery of specific cures. Until we can give our patients specific cures, therefore, we must by every force at our disposal combat the symptoms which cause suffering. We ease the pain with analgesics, we promote sleep with hypnotics, we create a feeling of hopefulness, we try to keep the mind and body at rest and at peace. We do all these things hoping that, by doing this, God will come to our aid and effect a cure, or if that is not to be, that our patient has a minimum of suffering.

To be more specific, consider the advice given to a man with a failing heart. Consider how much the successful carrying out of this advice involves social relationships with others. He must not hurry, he must not walk long distances but must ride in an automobile, he must not climb several flights of stairs but must use the elevator or, if there is not one, have his room on the ground floor. He must have rest periods, he must not over-eat, he must not be disturbed by argument or dissension, and so on and so forth—all advice *being* specific or specifically nonspecific. Consider how comparatively valueless would digitalis and nitroglycerin be without this advice as to the adjustment of environment and change in habits and how much the practical application of it may vary with each individual patient.<sup>10</sup>

I might go on and give many more examples from the hospital or private practice of physicians, but there is not the space. I have endeavored to show that human and social

factors can seldom be neglected in taking adequate care of patients. I have given examples of human and social factors occurring in various portions of the history and influencing diagnosis, treatment and prognosis. I have pointed out ways in which further knowledge and utilization of these factors may be obtained by the physician and aid him in the care of his patients.

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